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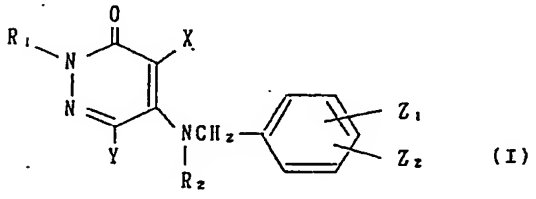
A request for correction of the originally filed description has been filed pursuant to Rule 88 EPC. A decision on the request will be taken during the proceedings before the Examining Division (Guidelines for Examination in the EPO, A-V, 2.2).

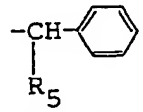
(54) **3(2H)pyridazinone, process for its preparation and antagonistic agent against SRS-A containing it.**

(57) A 3(2H)pyridazinone of the formula:

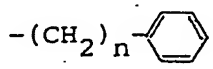


(I)

wherein R_1 is hydrogen, 2-propenyl or straight chained or branched C_1-C_4 alkyl; R_2 is hydrogen or C_1-C_3 alkyl; X is chlorine or bromine; Y is hydrogen, nitro, $-NHR_3$ wherein R_3 is hydrogen or straight chained or branched C_1-C_4 alkyl, $-AR_4$ wherein A is oxygen or sulfur and R_4 is hydrogen, straight chained or branched C_1-C_6 alkyl, C_3-C_6 alkenyl having one double bond, C_3-C_6 alkynyl having one triple bond, phenyl or



wherein R_5 is hydrogen or C_1-C_4 alkyl, or halogen; Z_1 is hydrogen, C_1-C_4 alkyl, $-OR_6$ wherein R_6 is hydrogen, straight chained or branched C_1-C_8 alkyl or



wherein n is an integer of from 1 to 4, $-N(R_7)_2$ wherein R_7 is C_1-C_4 alkyl, or halogen; Z_2 is C_1-C_4 alkyl, $-OR_6$ wherein R_6 is as defined above, $-N(R_7)_2$ wherein R_7 is as defined above, or halogen, provided that when R_1 is straight chained or branched C_2-C_4 alkyl, Y is not hydrogen and when R_1 is hydrogen, methyl or 2-propenyl, Y and R_2 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

EP 0 275 997 A1

Description

3(2H)PYRIDAZINONE, PROCESS FOR ITS PREPARATION AND ANTAGONISTIC AGENT AGAINST SRS-A CONTAINING IT

The present invention relates to a novel 3(2H)pridazinone which exhibits antagonism against slow reacting substance of anaphylaxis (SRS-A), a process for its preparation and a pharmaceutical composition containing it.

SRS-A is a chemical mediator released together with histamine, etc. by an allergic reaction and has pharmacological activity to contract bronchial smooth muscle strongly and continuously. It has long been known from such a phenomenal aspect. It was found in 1979 that SRS-A itself is a mixture of leukotriene C_4, D_4 and E_4 (generally called peptide leukotriene). Extensive researches have been conducted on SRS-A for its relationship with acosmia. As a result, the relationship of SRS-A with immediate type allergic deseases such as bronchial asthma, allergic rhinitics, urticaria and hay fever, has become clear. Further, the relationship of SRS-A with various inflammatory deseases, ischemic heart diseases, etc., has been suggested.
Therefore, a compound which exhibits antagonism against SRS-A, is expected to be useful as a prophylactic or therapeutic drug against the affections caused by either leukotriene C_4, D_4 or E_4, or by a mixture thereof.

As the antagonists against SRS-A, FPL-55712 and its structural analogues as well as some medicinal substtances, have been reported. (Agents and Actions, vol 9, p. 133-140 (1979), Annual Reports in Medicinal Chemistry, vol. 20, p. 71-81 (1985) and Agents and Actions, vol. 18, p. 332-341 (1986)) However, no instance of their clinical application has been reported.

Now, the relationship of the compounds of the present invention with compounds disclosed in published references will be described.

Canadian Patent No. 784,639 (hereinafter referred to as reference (a)) discloses 3(2H)pyridazinone derivatives having hydrogen, C_1-C_8 alkyl, phenyl or C_3-C_8 cycloalkyl at 2-position, chlorine or bromine at 4-position and benzylamino at 5-position. However, the reference has no Examples corresponding to the compounds of the present invention, and the application of the compounds disclosed in this reference (a) is restricted to a herbicide, and no mention is made as to their medical use or pharmacological activities.

Chemical Abstract, 62, 2773b, (Bull. Soc. Chim, France, 1964 (9) p 2124-32) (reference (b)) discloses 3(2H)pyridazinones having hydrogen or diethylaminoethyl at 2-position, chlorine at 4-position and benzylamino at 5-position. However, this reference (b) has no Examples corresponding to the compounds of the present invention, and it is silent about medical use or pharmacological activities.

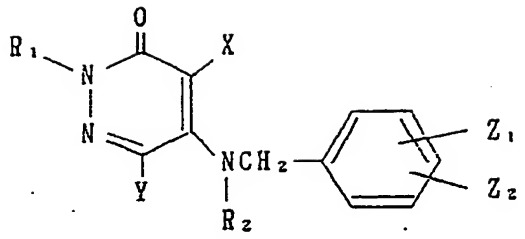
German Patent Application No. 1,670,169 published on November 5, 1970 (reference (c)) discloses 3(2)prydazinones having hydrogen or an aliphatic, cycloaliphatic, araliphatic or aromatic group at 2-position, chlorine or bromine at 4-position and aralkylamino at 5-position. This reference (c) discloses a process for the synthesis of pyridazinones including such compounds, their application to agricultural chemicals, their application as intermediates for medicines or dyestuffs, or their application as intermediates for various compounds. However, no mention is made to their pharmacological activities, and no specific examples are given for such compounds. Further, such compounds are not specifically described.

Angew. Chem. International Edition, vol. 4, p. 292-300 (1965) (reference (d)) discloses 3(2H)pyridazinones having hydrogen at 2-position, chlorine at 4-position and N-methyl-benzylamino at 5-position. However, this reference (d) has no Examples corresponding to the compounds of the present invention, and no mention is made as to medical use or pharmacological activities.

The present inventors have conducted extensive researches with an object to find compounds which exhibit antagonism against SRS-A. They have found that 5-substituted benzylamino-3(2H)pyridazinone derivatives having various functional groups and substitution modes, attain the above object, and have already filed patent applications (Japanese Unexamined Patent Publicaiton No. 267560/1986 (reference (e)) and Japanese Unexamined Patent Publication No. 075179/1986 (reference (f)). However, the compounds disclosed in these references (e) and (f) are restricted to 3(2H)pyridazinones having no substituent at 6-position (hydrogen). Further, reference (f) discloses 5-substituted benzylamino-3(2H)pyridazinone derivatives having hydrogen or 2-propenyl at 2-position. However, the amino at 5-position is secondary amino in all cases, and no compound having tertiary amino is included therein.

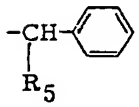
The present inventors have then conducted extensive researches on compounds having antagonistic activities against SRS-A, and it has been surprisingly found that 3(2H)pyridazinones of the formula I and their pharmacologically acceptable salts are more excellent in the antagonistic activities against SRS-A, and that they are useful as active ingredients for prophylactic or therapeutic drugs against deseases caused by leukotriene C_4, D_4 or E_4, or by a mixture thereof which is a component of SRS-A. The present invention has been accomplished on the basis of this discovery.

The present invention provides a 3(2H)pyridazinone of the formula:

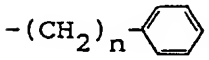


(I)

wherein R_1 is hydrogen, 2-propenyl or straight chained or branched C_1-C_4 alkyl; R_2 is hydrogen or C_1-C_3 alkyl; X is chlorine or bromine; Y is hydrogen, nitro, -NHR_3 wherein R_3 is hydrogen or straight chained or branched C_1-C_4 alkyl, -AR_4 wherein A is oxygen or sulfur and R_4 is hydrogen, straight chained or branched C_1-C_6 alkyl, C_3-C_6 alkenyl having one double bond, C_3-C_6 alkynyl having one triple bond, phenyl or



wherein R_5 is hydrogen or C_1-C_4 alkyl, or halogen; Z_1 is hydrogen, C_1-C_4 alkyl, -OR_6 wherein R_6 is hydrogen, straight chained or branched C_1-C_8 alkyl or



wherein n is an integer of from 1 to 4, -$N(R_7)_2$ wherein R_7 is C_1-C_4 alkyl, or halogen; Z_2 is C_1-C_4 alkyl, -OR_6 wherein R_6 is as defined above, -$N(R_7)_2$ wherein R_7 is as defined above, or halogen, provided that when R_1 is straight chained or branched C_2-C_4 alkyl, Y is not hydrogen and when R_1 is hydrogen, methyl or 2-propenyl, Y and R_2 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

Now, the present invention will be descirbed with reference to the preferred embodiment. Specific examples of substituents R_1, R_2, X, Y, Z_1 and Z_2 in the formula I will be desribed. However, it should be understood that the present invention is by no means restricted to such specific examples. In the following substituents, "n" means normal, "i" means iso, "sec" means secondary and "t" means tertiary.

R_1 includes hydrogen, 2-propenyl, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. Among them, preferred is hydrogen, ethyl or i-propyl. More preferred is hydrogen.

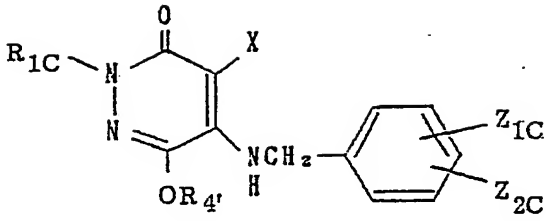
R_2 includes hydrogen, methyl, ethyl and n-propyl. Preferred is hydrogen.

X includes chlorine and bromine.

Y includes hydrogen, nitro, amino, -NHR_3 wherein R_3 is methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl or sec-butyl, -AR_4 wherein AR_4 is a combination of A being oxygen or sulfur and R_4 being hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, n-hexyl, i-hexyl, sec-hexyl, 2-propenyl, 2-butenyl, 2-pentenyl, 2-hexenyl, 2-methyl-2-propenyl, 2-ethyl-2-propenyl, 2-n-propyl-2-propenyl, 1-methyl-2-propenyl, 2-ethyl-2-propenyl, 2-propynyl(propargyl), 2-butynyl, 2-pentynyl, 1-methyl-2-propynyl, 2-ethyl-2-propynyl, benzyl, α-methylbenzyl, α-ethylbenzyl, α-n-propylbenzyl or α-n-butylbenzyl), fluorine, chlorine, bromine and iodine. Among them, preferable examples of Y are nitro and -OR_4 wherein R_4 is the alkyl, alkenyl, alkynyl, benzyl or substituted benzyl as specified above in the definition of AR_4.

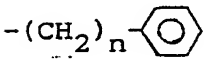
Z_1 includes hydrogen, methyl, ethyl, n-propyl, n-butyl, hydroxyl, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, n-pentoxy, n-hexyloxy, n-heptyloxy, n-octyloxy, benzyloxy, 2-phenylethoxy, 3-phenylpropoxy, 4-phenylbutoxy, dimethylamino, diethyamino, di-n-propylamino, di-n-butylamino, fluorine, chlorine, bromine and iodine. Z_2 includes the same substituents as mentioned for Z_1 except that it does not include hydrogen. Among possible combinations of Z_1 and Z_2, preferred is a combination of the above-mentioned alkyl and/or alkoxy groups such as 3,4-dialkoxy or 3-alkyl-4-alkoxy. A more preferable combination of Z_1 and Z_2 is 3-alkoxy-4-methoxy or 3-alkyl-4-methoxy.

Among the compounds of the formula I, preferable compounds are represented by the formula IC:



(IC)

wherein R_{1C} is hydrogen, ethyl or i-propyl; X is chlorine or bromine; R_4' is the same substituent as R_4 as defined in the formula I except that it does not include hydrogen; Z_{1C} is hydrogen or $-OR_6$ wherein R_6 is straight chained C_1-C_8 alkyl or



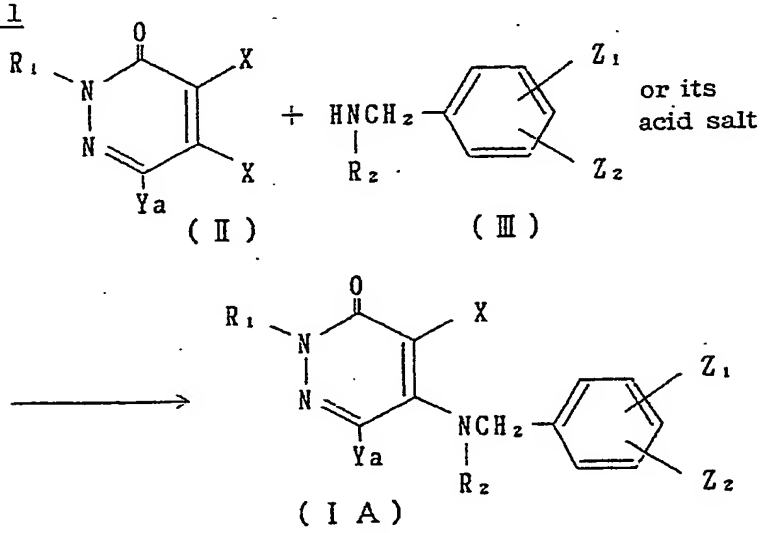
wherein n is an integer of 1 to 4; and Z_{2C} is $-OR_6$ wherein R_6 is as defined above.

Among the compounds of the formula IC, particularly preferred are Compound No. 56, 57, 58, 60, 61, 63, 64, 65, 66, 67, 68, 69, 84, 85, 86, 88, 89, 90 and 91 as identified in Table 5.

The compounds of the formula I may have E- and Z-form isomers depending upon the presence of a double bond, and optical isomers or stereoisomers depending upon the presence of 1 to 3 asymmetric carbon. The present invention includes all these isomers and mixtures thereof.

Now, the process for producing the compounds of the present invention will be described. The compounds of the formula I of the present invention can be prepared by the following processes 1 to 5.

Process 1



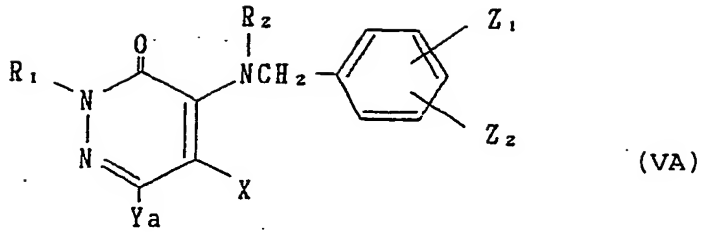
(II) (III) or its acid salt

(IA)

In the above formulas, R_1, R_2, X, Z_1 and Z_2 are as defined above with respect to the formula I; Ya is hydrogen, nitro, amino or $-OR_4$ wherein R_4 is as defined above with respect to the formula I, or halogen.

Process 1 comprises reacting a 4,5-dihalo-3(2H)pridazinone compound of the formula II with a benzylamine derivative of the formula III or its acid salt in an inert solvent, if necessary in the presence of a dehydrohalogenating agent to obtain a compound of the formula IA, which is a compound of the formula I having Ya at 6-position wherein Ya is as defined above.

In process 1, a compound of the formula VA:



(VA)

wherein all symbols are as defined above, which is a position isomer of the compound of the formula IA having benzyl amino at 4-position, is formed as a by-product.

The production ratios of the compounds IA and VA depend primarily upon the polarity of the solvent used. Namely, when a solvent of high polarity is used, the production ratio of the compound IA of the present invention tends to be high. Conversely, when a solvent of low polarity such as benzene, toluene or hexane is used, the production ratio of the compound VA tends to be high. Therefore, as a suitable solvent for efficient production of the compound IA of the present invention, an ether solvent such as tetrahydrofuran or 1,4-dioxane, an amide solvent such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide or N-methylpyrrolidone, acetonitrile, dimethylsulfoxide, an alcohol solvent such as methanol, ethanol or propanol, an organic amine solvent such as pyridine or triethylamine, or water, or a solvent mixture thereof, may be mentioned. The desired 5-benzylamino isomer IA can readily be separated and purified from the mixture of the 4- and 5-benzylamino isomers by conventional methods known per se in organic synthesis, such as fractional recrystallization or various silica gel chromatography.

During the reaction, hydrogen chloride or hydrogen bromide is generated. It is usually advantageous to add to the reaction system a dehydrohalogenating agent which traps such a hydrogen halide.

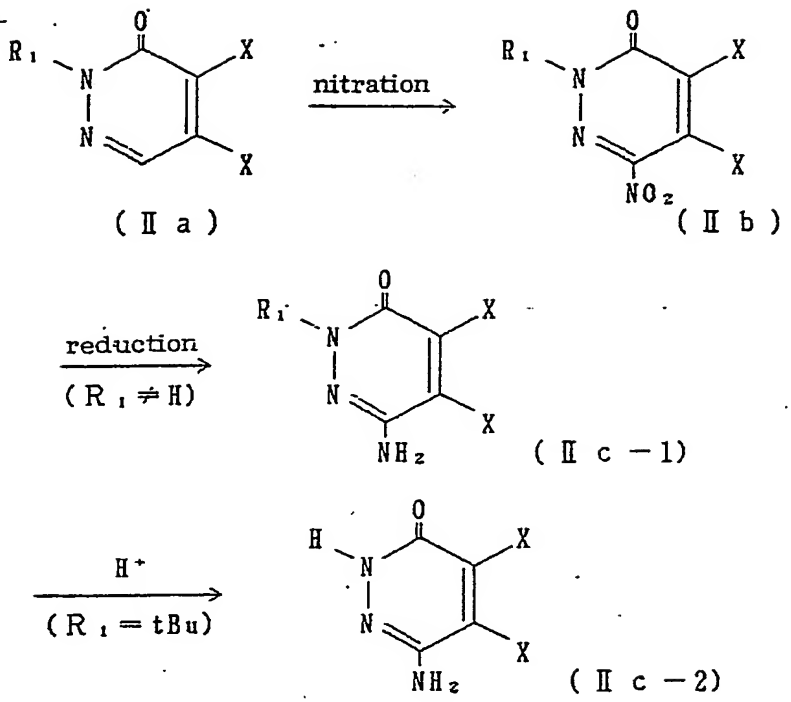
Any dehydrohalogenating agent may be used so long as it does not adversely affect the reaction and is capable of trapping a hydrogen halide. As such a dehydrohalogenating agent, an inorganic base such as potassium carbonate, sodium carbonate, potassium hydrogencarbonate, or sodium hydrogencarbonate, or an organic base such as N,N-dimethylaniline, N,N-diethylaniline, trimethylamine, triethylamine or pyridine, may be mentioned. Otherwise, the benzylamine III starting material itself may be used in an excessive amount as the hydrogen halide trapping agent. This gives preferred results in many cases. The reaction temperature may be within a range of from 10°C to the boiling point of the solvent used for the reaction.

The molar ratio of the starting materials may optionally be set. However, the benzylamine derivative of the formula III may be used in an amount of from 1 to 10 moles relative to one mole of the 4,5-dihalo-3(2H)pyridazinone derivative of the formula II, and usually, it is enough that from 1.2 to 5 moles thereof is used.

The 4,5-dihalo-3(2H)pyridazinone derivative II as one of the starting materials can be prepared by a conventional process or by an application of a conventional organic reaction as described below. Namely, the compound of the formula IIa or the formula II wherein Ya is hydrogen, can be prepared by the methods disclosed in the above-mentioned references (e) and (f).

Further, the compound of the formula IIb or the formula II wherein Ya is nitro, can be prepared from the compound IIa by the methods disclosed in Japanese Examined Patent Publication Nos. 1299/1967 and 20096/1969 as shown in Process 1-(1).

Process 1-(1)

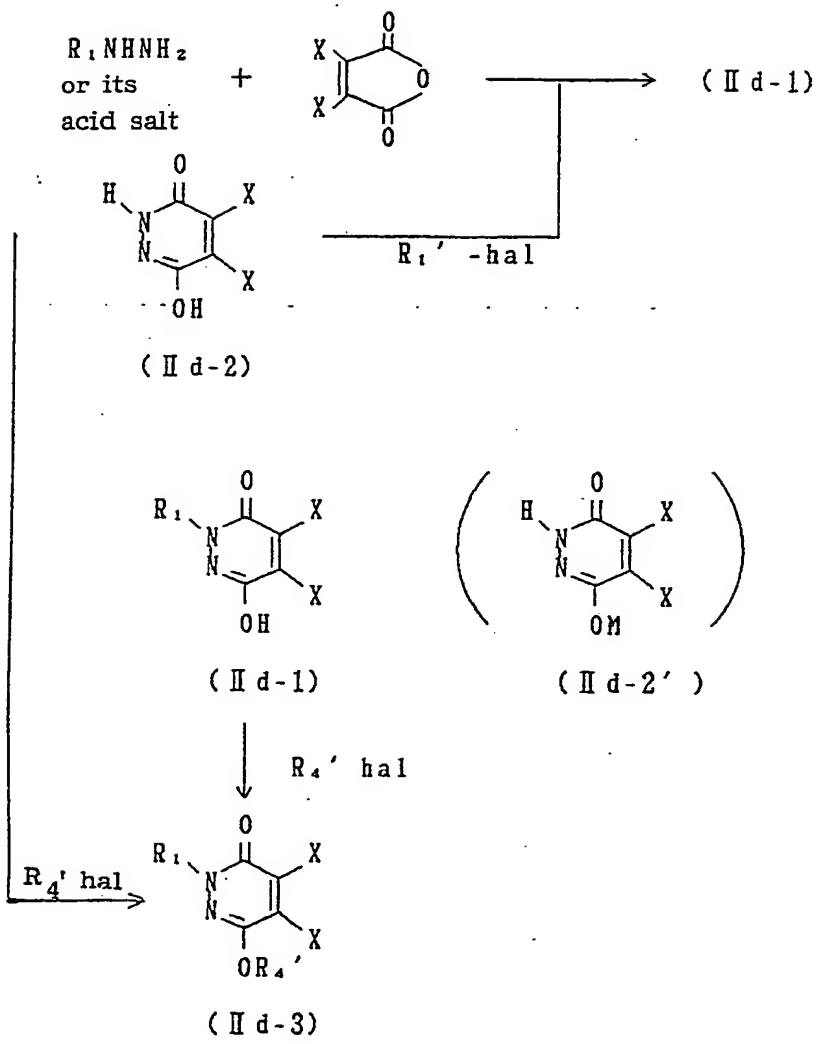


In the above formulas, R_1 and X are as defined above with respect to the formula I.

The compounds of the formulas IIc-1 and IIc-2 wherein Ya is amino can be prepared, respectively, by the method disclosed in Japanese Examined Patent Publication No. 5298/1969 or by a method of treating the 6-amino-4,5-dihalo-3(2H)pyridazinone derivative wherein R_1 is t-butyl, with a mineral acid such as hydrochloric acid or sulfuric acid or an organic acid such as trifluoroacetic acid or methanesulfonic acid, to remove t-butyl at 2-position.

Further, the compounds of the formulas IId-1 and IId-2 wherein Ya is hydroxyl, and the compound of the formula IId-3 wherein Ya is alkoxy, can easily be prepared by the method as shown in Process 1-(2). Namely, the 6-hydroxy-4,5-dihalopyridazinone derivative can usually be prepared by the ring closure condensation reaction of a hydrazine or its acid salt with a dihalomaleic anhydride. Further, the compound having a substituent at 2-position, can be prepared by employing a process using the compound of the formula IId-2 as the intermediate.

Process 1-(2)

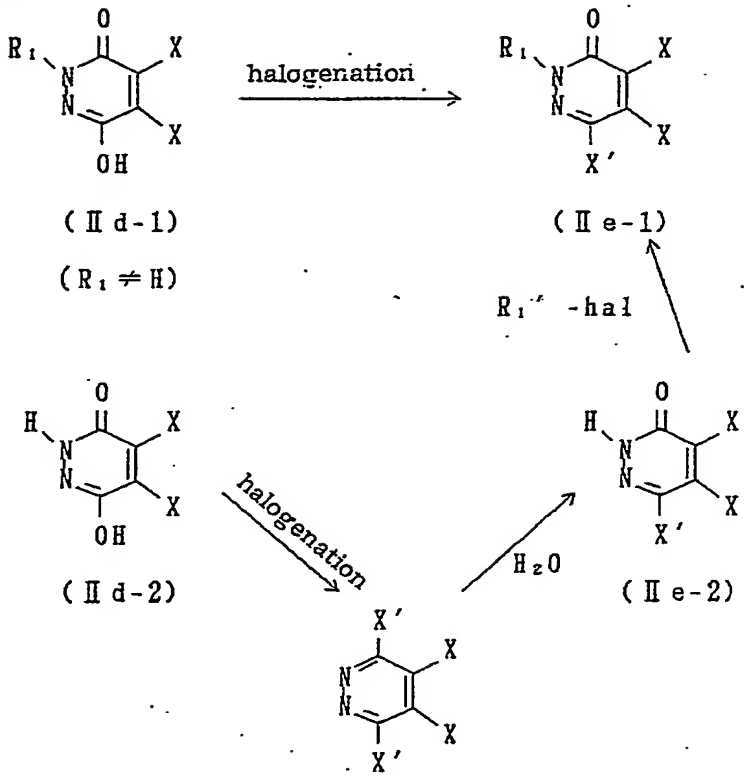


In the above formulas, R_1 and X are as defined above with respect to the formula I, R_1' is straight chained or branched C_1-C_4 alkyl or 2-propenyl, R_4' is the same substituent as R_4 defined above with respect to the foumula I except that it does not include hydrogen, hal is chlorine, bromine or iodine, and M is alkali metal.

With respect to the reaction effeciency or the operation, the former process is usually advantageous. However, it is advantageous to employ the latter process when the hydrazine starting material is not readily available as a commercial product and it can not easily or economically be produced. Next, the 6-alkoxy-4,5-dihalo-3(2H)pyridazinone derivative of the formula IId-3, can be prepared by reacting the 6-hydroxy derivative of the formula IId-1 or IId-2, with a halogeno derivative of the formula R_4'-hal in the presence of a conventional base. Here, a 2-R_4' form (IId-1, $R_1 = R_4'$) may be formed as a by-product in addition to the desired O-R_4' form (IId-3, $R_1 = H$) in the reaction of the compound IId-2 with R_4'-hal. In such a case, good results are often obtained by using a method wherein the reaction is conducted by restricting the ammount of the base to a level of from 1 to 1.2 equivalent, or a method wherein the compound IId-2 is treated with about the same mol of caustic alkali to isolate an alkali metal salt IId-2' and the isolated alkali metal salt is reacted with R_4'-hal in a nonaqueous solvent system.

Further, compounds of the formula IIe-1 and IIe-2, which are compounds of the formula II wherein Ya is a halogen, can be prepared by using or applying the method disclosed in Monatshefte fur Chemie, vol 99, 15 (1968) or Japanese Examined Patent Publication No. 24029/1972.

Process 1 - (3)

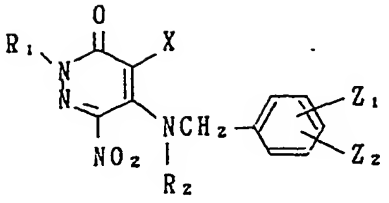


In the above formulas, R_1'-hal and X are as defined above in Process 1-(2), and X' is halogen.

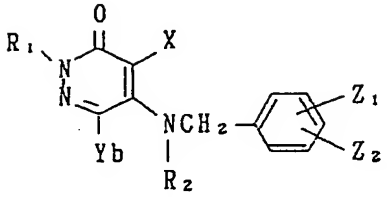
Among the benzylamines of the formula III as another starting material in Process I, those hardly available as commercial products, can readily be prepared by the method disclosed in reference (e).

Process 2

(1)

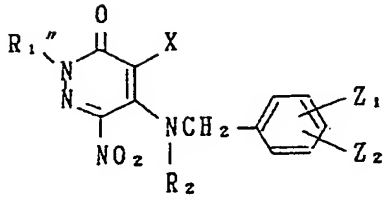


(IB-a)

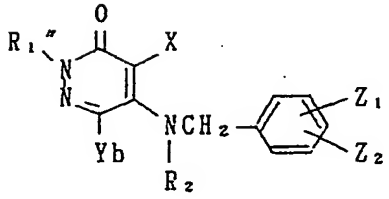


(IB)

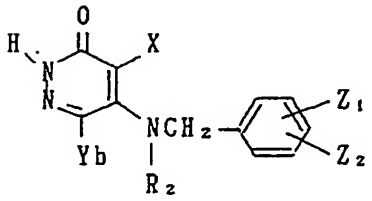
(2)



(IB-b)



(IB-c)



(IB')

In the above formulas, R_1, R_2, X, Z_1 and Z_2 are as defined above with respect to the formula I, M is alkali metal, Yb is $-NHR_3$ or $-AR_4$ wherein R_3, A and R_4 are as defined above with respect to the formula I, and R_1" is

a protective group.

Process 2 comprises a substitution reaction of nitro between a 6-nitro-5-benzylamino derivative of the formula IB-a or IB-b and an alkali metal salt of the formula IV i.e. M+Yb−, to obtain a 6-substituted-5-benzylamino derivative of the formula IB or IB'.

Among the desired compounds, a compound having hydrogen at 2-position of pyridazinone, can be prepared by the direct route as shown in Process 2-(1), or by a route as shown in Process 2-(2) which comprises converting the 6-nitro derivative of the formula IB-b protected at 2-position with R_1'' as a starting material to a compound of the formula IB-c and then removing the protective group R_1'', to obtain the desired compound.

As the protective group of R_1'', 2-trimethylsilylethoxymethyl ($Me_3Si\frown OCH_2$), methoxymethyl ($MeOCH_2$-) or CO_2R wherein R is lower alkyl, is preferably used. The removal of the protective group R_1'' can easily be conducted by a conventional method for the removal of such protective groups.

Here, the alkali metal of the formula M includes lithium, sodium and potassium.

Therefore, an alkali metal salt used as a nucleophilic agent in Process 2 includes a metal amide, an alkali metal hydroxide, a metal alkoxide, an alkali metal hydrosulfide and a metal mercaptide defined by above R_3 or R_4.

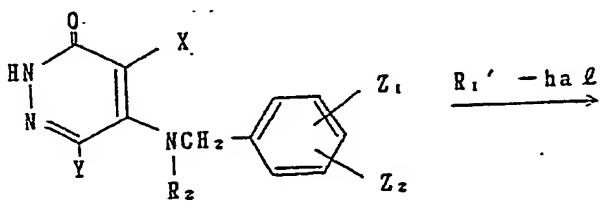
There is no particular restriction as to the reaction solvent so long as it is inert to the reaction, though it may be suitably selected depending upon the type of the alkali metal salt used for the reaction. For example, in the case of using a metal amide, liquid ammonia or an ether solvent such as diethyl ether, tetrahydrofuran or 1,4-dioxane, is preferably used. In the case of using an alkali metal hydroxide or alkali metal hydrosulfide, good results are often obtained by using an alcohol solvent such as methanol, ethanol, n-propanol or n-butanol, dimethylsulfoxide, an amide solvent such as formamide, N,N-dimethylformamide or N,N-dimethylaceteamide or a polar solvent such as water. In the case of using a metal alkoxide or metal mercaptide, the reaction is usually conducted in the corresponding alcohol or mercaptan. However, the reaction can be conducted in the above-mentioned ether solvent or in a medium including a benzene solvent such as benzene or toluene.

The reaction temperature varies depending upon the reactants used. It is usually within a range of from -78°C to the boiling point of the solvent used for the reaction.

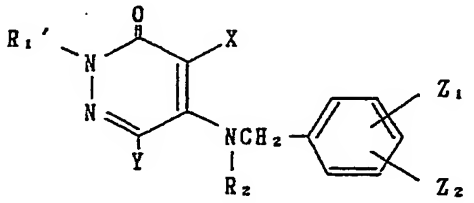
The molar ratio of the starting materials can be optionally determined, and it is sufficient that the alkali metal salt of the formula IV is used in an amount of from 1.2 to 10 mols relative to one mol of the 6-nitro-5-benzylamino derivative of the formula IB-a or IB-b.

The desired compound can readily be isolated and purified by a method known per se in organic syntheses such as recrystallization, various silica gel chromatography or distillation.

Process 3



(I − a)



(I − b)

In the above formulas, R_2, X, Y, Z_1 and Z_2 are as defined above with respect to the formula I, and R_1' and hal are as defined above in Process 1-(2).

Process 3 is a process which comprises reacting a compound of the formula I-a i.e. a compound of the formula I having hydrogen at 2-position of pyridazinone, with a halogeno derivative of the formula R_1'-hal, to obtain a 2-substituted compound of the formula I-b.

Process 3 is usually conducted in the presence of an inorganic base such as potassium carbonate, sodium carbonate, lithium carbonate, potassium hydrogencarbonate, sodium hydrogencarbonate or lithium hydroxide. Further, in the case where R_2 is alkyl in the formula I-a, it is possible to use a metal hydride such as

sodium hydride or n-butyl lithium in addition to the above inorganic base.

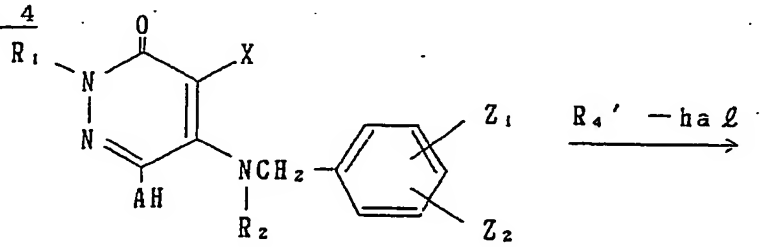
In the case of using the inorganic base, a ketone solvent such as acetone, methyl ethyl ketone or diethyl ketone, an amide solvent such as formamide, N,N-dimethylformamide or N,N-dimethylaceteamide, an alcohol solvent such as methanol or ethanol, or water, or a mixture thereof, is preferred as the reaction solvent, and in the case of using the metal hydride, an ether solvent is preferably used.

In the case of using the inorganic base, the reaction temperature is usually within a range of from 0°C to the boiling point of the solvent, and in the case of using the metal hydride, it is usually within a range of from -78 to 60°C.

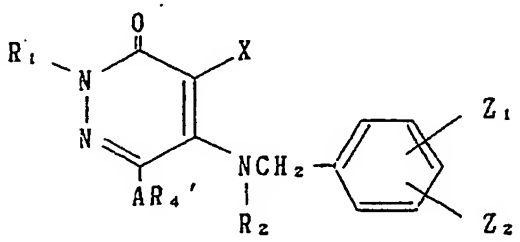
The molar ratio of the starting materials may optionally be determined. However, the halogen compound of the formula R_1-hal is used usually in an amount of from 1 to 5 mols relative to one mol of the compound of the formula I-a.

The desired compound can be isolated and purified in accordance with the method as described with respect to Process 2.

Process 4



(I C — a)



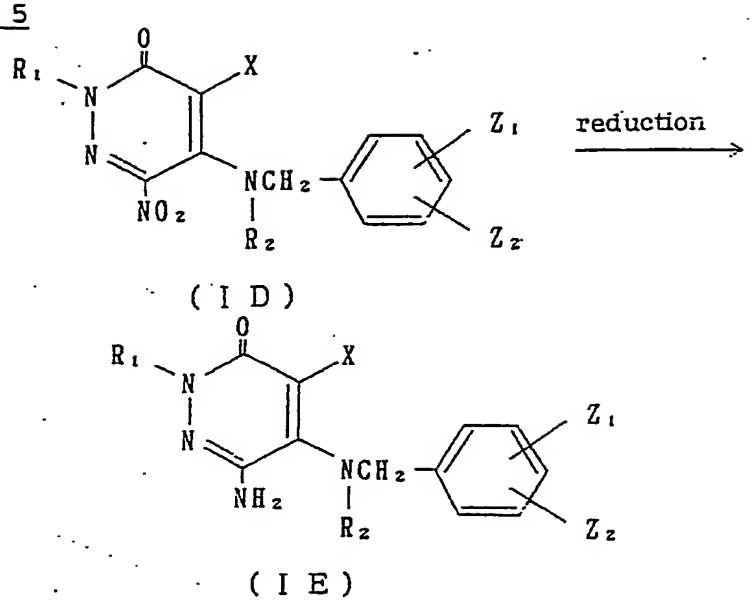
(I C — b)

In the above formulas, R_1, R_2, X, A, Z_1 and Z_2 are as defined above with respect to the formula I, and R_4' and hal are as defined above in Process 1-(2).

Process 4 is a process which comprises reacting a 6-hydroxy or 6-mercapto derivative of the foumula IC-a with a halogeno derivative of the formula R_4'-hal, to obtain a 6-alkoxy or 6-substituted mercapto derivative of the formula IC-b.

For process 4, it is possible to employ the same reaction condition as in the above Process 1-(2) or Process 3.

Process 5



(I D)

(I E)

In the above formulas, all symbols are as defined above with respect to the formula I.

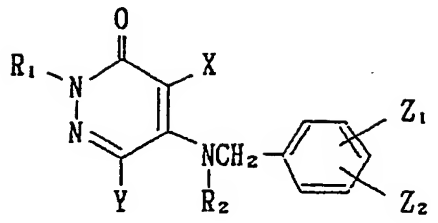
Process 5 is a process which comprises a reduction reaction of a 6-nitro derivative of the formula ID, to obtain a 6-amino derivative of the formula IE.

For the reduction, a method of using sodium hydrosulfite, sodium sulfide or the like, or a method of using a metal such as iron, zinc, tin or the like in the presence of acid, may be employed. For this reduction reaction, it is desired to avoid a high temperature or a strong acidic condition with a high concentration of an acid, because a functional group such as halogen or benzyl, in the compound ID, will readily be reduced or eliminated under a strong acidic condition.

A protic solvent such as methanol, ethanol, n-propanol, acetic acid or water, or a mixture thereof, is usually preferably used as the solvent for the reaction. The reaction temperature may be within a range of from -10 to 50°C. In many cases, the reaction proceeds smoothly.

In addition to those described in the Examples given hereinafter, the following compounds (in Table 1) may be mentioned as the compounds of the present invention. In the following compounds, "n" means normal, "i" means iso, "sec" means secondary, "Me" means methyl, "Et" means ethyl, "Pr" means propyl, "Bu" means butyl, "Pen" means pentyl, "Hex" means hexyl, "Hep" means heptyl, "Oct" means octyl, and "Ph" means phenyl.

Table 1



R_1	R_2	X	Y	Z_1	Z_2
H	Me	Cℓ	OEt	3-OEt	4-OMe
H	Me	Br	OEt	3-OEt	4-OMe
H	Me	Cℓ	OEt	3-O-n-Pr	4-OMe
H	Me	Br	OEt	3-O-n-Pr	4-OMe
H	Me	Cℓ	O-i-Pr	3-OEt	4-OMe
H	Me	Br	O-i-Pr	3-OEt	4-OMe
H	Me	Cℓ	O-i-Pr	3-Cℓ	4-OMe
H	Me	Br	O-i-Pr	3-Cℓ	4-OMe
H	Me	Cℓ	Cℓ	3-OEt	4-OMe
H	Me	Br	Cℓ	3-OEt	4-OMe
H	Me	Cℓ	OEt	3-n-Pr	4-OMe
H	Me	Cℓ	OEt	3-O-n-Bu	4-OMe
H	Me	Br	OEt	3-O-n-Bu	4-OMe
H	Me	Cℓ	OEt	3-O-n-Pen	4-OMe
H	Me	Br	OEt	3-O-n-Pen	4-OMe
H	Me	Cℓ	OEt	3-O$(CH_2)_2$Ph	4-OMe
H	Me	Br	OEt	3-O$(CH_2)_2$Ph	4-OMe
Et	Me	Cℓ	OEt	3-OEt	4-OMe

R_1	R_2	X	Y	Z_1	Z_2
Et	Me	Br	OEt	3-OEt	4-OMe
Et	Me	Cℓ	OEt	3-O-n-Pr	4-OMe
Et	Me	Br	OEt	3-O-n-Pr	4-OMe
H	H	Cℓ	OMe	3-OMe	4-OMe
H	H	Br	OMe	3-OEt	4-OMe
H	H	Cℓ	OMe	3-O-n-Pr	4-OMe
H	H	Br	OMe	3-O-n-Pr	4-OMe
H	H	Cℓ	OMe	3-O-n-Bu	4-OMe
H	H	Br	OMe	3-O-n-Bu	4-OMe
H	H	Cℓ	OMe	H	4-OEt
H	H	Br	OMe	H	4-OEt
H	H	Cℓ	OMe	H	4-Et
H	H	Br	OMe	H	4-Et
H	H	Cℓ	OMe	3-n-Pr	4-OMe
H	H	Br	OMe	3-n-Pr	4-OMe
H	H	Cℓ	OMe	3-OEt	4-Cℓ
H	H	Br	OMe	3-OEt	4-Cℓ
H	H	Cℓ	SEt	3-OMe	4-OMe
H	H	Br	OEt	3-OMe	4-OMe
H	H	Cℓ	OEt	2-OMe	4-OMe
H	H	Br	OEt	2-OMe	4-OMe
H	H	Cℓ	OEt	2-Me	4-Me
H	H	Br	OEt	2-Me	4-Me
H	H	Cℓ	OEt	3-Cℓ	4-Cℓ
H	H	Br	OEt	3-Cℓ	4-Cℓ

R_1	R_2	X	Y	Z_1	Z_2
H	H	Cℓ	OEt	3-Et	H
H	H	Br	OEt	3-Et	H
H	H	Cℓ	SEt	3-OEt	4-OMe
H	H	Br	OEt	3-OEt	4-OMe
H	H	Cℓ	SEt	3-O-n-Pr	4-OMe
H	H	Br	OEt	3-O-n-Pr	4-OMe
H	H	Cℓ	SEt	3-O-n-Bu	4-OMe
H	H	Br	OEt	3-O-n-Bu	4-OMe
H	H	Cℓ	OEt	3-O-n-Pen	4-OMe
H	H	Br	OEt	3-O-n-Pen	4-OMe
H	H	Cℓ	OEt	3-O-n-Hex	4-OMe
H	H	Br	OEt	3-O-n-Hex	4-OMe
H	H	Cℓ	OEt	3-O-n-Hep	4-OMe
H	H	Br	OEt	3-O-n-Hep	4-OMe
H	H	Cℓ	OEt	3-O-n-Oct	4-OMe
H	H	Br	OEt	3-O-n-Oct	4-OMe
H	H	Cℓ	OEt	$3\text{-O}(CH_2)_2Ph$	4-OMe
H	H	Br	OEt	$3\text{-O}(CH_2)_2Ph$	4-OMe
H	H	Cℓ	OEt	$3\text{-O}(CH_2)_3Ph$	4-OMe
H	H	Br	OEt	$3\text{-O}(CH_2)_3Ph$	4-OMe
H	H	Cℓ	SMe	3-OMe	4-OMe
H	H	Br	O-i-Pr	3-OMe	4-OMe
H	H	Cℓ	O-i-Pr	2-OMe	4-OMe
H	H	Br	O-i-Pr	2-OMe	4-OMe
H	H	Cℓ	O-i-Pr	2-Me	4-Me

R_1	R_2	X	Y	Z_1	Z_2
H	H	Br	O-i-Pr	2-Me	4-Me
H	H	Cℓ	O-i-Pr	3-Et	4-Cℓ
H	H	Cℓ	O-i-Pr	3-Et	4-N(Me)$_2$
H	H	Cℓ	O-i-Pr	3-Cℓ	4-Cℓ
H	H	Br	O-i-Pr	3-Cℓ	4-Cℓ
H	H	Cℓ	O-i-Pr	H	4-OEt
H	H	Br	O-i-Pr	H	4-OEt
H	H	Cℓ	SMe	3-OEt	4-OMe
H	H	Br	O-i-Pr	3-OEt	4-OMe
H	H	Cℓ	O-i-Pr	3-OEt	4-Cℓ
H	H	Br	O-i-Pr	3-OEt	4-Cℓ
H	H	Cℓ	O-i-Pr	3-OEt	4-N(Me)$_2$
H	H	Br	O-i-Pr	3-OEt	4-N(Me)$_2$
H	H	Cℓ	SMe	3-O-n-Pr	4-OMe
H	H	Br	O-i-Pr	3-O-n-Pr	4-OMe
H	H	Cℓ	SMe	3-O-n-Bu	4-OMe
H	H	Br	O-i-Pr	3-O-n-Bu	4-OMe
H	H	Cℓ	O-i-Pr	3-O-n-Pen	4-OMe
H	H	Br	O-i-Pr	3-O-n-Pen	4-OMe
H	H	Cℓ	SMe	3-O-n-Hex	4-OMe
H	H	Br	O-i-Pr	3-O-n-Hex	4-OMe
H	H	Cℓ	O-i-Pr	3-O-n-Hep	4-OMe
H	H	Br	O-i-Pr	3-O-n-Hep	4-OMe
H	H	Cℓ	O-i-Pr	3-O-n-Oct	4-OMe
H	H	Br	O-i-Pr	3-O-n-Oct	4-OMe

R_1	R_2	X	Y	Z_1	Z_2
H	H	Cℓ	O-i-Pr	3-O$(CH_2)_2$Ph	4-OMe
H	H	Br	O-i-Pr	3-O$(CH_2)_2$Ph	4-OMe
H	H	Cℓ	Cℓ	3-O$(CH_2)_2$Ph	4-OMe
H	H	Br	Cℓ	3-OEt	4-OMe
H	H	Cℓ	Br	3-OEt	4-OMe
H	H	Br	Br	3-OEt	4-OMe
H	H	Cℓ	F	3-OEt	4-OMe
H	H	Br	F	3-OEt	4-OMe
H	H	Cℓ	NHMe	3-OEt	4-OMe
H	H	Br	NHMe	3-OEt	4-OMe
H	H	Cℓ	NHEt	3-OEt	4-OMe
H	H	Br	NHEt	3-OEt	4-OMe
H	H	Cℓ	Cℓ	3-OMe	4-OMe
H	H	Br	Cℓ	3-O-n-Pr	4-OMe
H	H	Cℓ	NHMe	3-O-n-Pr	4-OMe
H	H	Br	NHMe	3-O-n-Pr	4-OMe
H	H	Cℓ	O-n-Pr	3-OMe	4-OMe
H	H	Br	O-n-Pr	3-OMe	4-OMe
H	H	Cℓ	O-i-Bu	3-OMe	4-OMe
H	H	Br	O-i-Bu	3-OMe	4-OMe
H	H	Cℓ	O-n-Pr	3-OEt	4-OMe
H	H	Br	O-n-Pr	3-OEt	4-OMe
H	H	Cℓ	O-i-Bu	3-OEt	4-OMe
H	H	Br	O-i-Bu	3-OEt	4-OMe
H	H	Cℓ	O-n-Pr	3-O-n-Pr	4-OMe

R_1	R_2	X	Y	Z_1	Z_2
H	H	Br	O-sec-Bu	3-OMe	4-OMe
H	H	Br	O-sec-Bu	3-OEt	4-OMe
H	H	Cℓ	O-sec-Bu	3-O-n-Pr	4-OMe
H	H	Br	O-sec-Bu	3-O-n-Pr	4-OMe
H	H	Cℓ	O-sec-Bu	3-O-n-Bu	4-OMe
H	H	Br	O-sec-Bu	3-O-n-Bu	4-OMe
H	H	Br	O-n-Pr	3-O-n-Pr	4-OMe
H	H	Cℓ	O-i-Bu	3-O-n-Pr	4-OMe
H	H	Br	O-i-Bu	3-O-n-Pr	4-OMe
H	H	Cℓ	O-n-Pr	3-O-n-Bu	4-OMe
H	H	Br	O-n-Pr	3-O-n-Bu	4-OMe
H	H	Cℓ	O-i-Bu	3-O-n-Bu	4-OMe
H	H	Br	O-i-Bu	3-O-n-Bu	4-OMe
H	H	Cℓ	O-n-Pr	3-O$(CH_2)_2$Ph	4-OMe
Et	H	Br	OMe	3-O-n-Pr	4-OMe
Et	H	Cℓ	OEt	3-OMe	4-OMe
Et	H	Br	OEt	3-OMe	4-OMe
Et	H	Br	OEt	3-O-n-Pr	4-OMe
Et	H	Cℓ	OEt	3-O-n-Bu	4-OMe
Et	H	Br	OEt	3-O-n-Bu	4-OMe
i-Pr	H	Cℓ	OEt	2-OMe	4-OMe
i-Pr	H	Br	OEt	2-OMe	4-OMe
i-Pr	H	Cℓ	OEt	3-OMe	4-OMe
i-Pr	H	Br	OEt	3-OMe	4-OMe
i-Pr	H	Cℓ	OEt	3-OEt	4-OMe

R_1	R_2	X	Y	Z_1	Z_2
i-Pr	H	Br	OEt	3-OEt	4-OMe
i-Pr	H	Cℓ	OEt	3-O-n-Bu	4-OMe
i-Pr	H	Br	OEt	3-O-n-Pr	4-OMe
Et	H	Cℓ	OEt	2-Me	4-Me
Et	H	Br	OEt	2-Me	4-Me
$-CH_2CH=CH_2$	H	Cℓ	OEt	3-OEt	4-OMe
$-CH_2CH=CH_2$	H	Br	OEt	3-OEt	4-OMe
i-Pr	H	Cℓ	O-i-Pr	3-OEt	4-OMe
i-Pr	H	Br	O-i-Pr	3-OEt	4-OMe
i-Pr	H	Cℓ	O-i-Pr	3-O-n-Bu	4-OMe
i-Pr	H	Br	O-i-Pr	3-O-n-Pr	4-OMe
$-CH_2CH=CH_2$	H	Cℓ	O-i-Pr	3-OEt	4-OMe
$-CH_2CH=CH_2$	H	Br	O-i-Pr	3-OEt	4-OMe
Me	H	Cℓ	O-i-Pr	3-OEt	4-OMe
Me	H	Br	O-i-Pr	3-OEt	4-OMe
Me	H	Cℓ	O-i-Pr	3-O-n-Pr	4-OMe
Me	H	Br	O-i-Pr	3-O-n-Pr	4-OMe
Et	H	Cℓ	O-n-Pr	3-OEt	4-OMe
Et	H	Br	O-n-Pr	3-OEt	4-OMe
Et	H	Cℓ	O-n-Pr	3-OMe	4-OMe
Et	H	Br	O-n-Pr	3-O-n-Pr	4-OMe
Et	H	Cℓ	O-i-Bu	3-OEt	4-OMe
Et	H	Br	O-i-Bu	3-OEt	4-OMe
Et	H	Cℓ	Cℓ	3-OEt	4-OMe
Et	H	Cℓ	Br	3-OEt	4-OMe

R_1	R_2	X	Y	Z_1	Z_2
Et	H	Br	Cℓ	3-OEt	4-OMe
Et	H	Br	Br	3-OEt	4-OMe
Et	H	Cℓ	Cℓ	3-OMe	4-OMe
Et	H	Br	Cℓ	3-O-n-Pr	4-OMe
i-Pr	H	Cℓ	Cℓ	3-OEt	4-OMe
i-Pr	H	Br	Cℓ	3-OEt	4-OMe
Et	H	Cℓ	NHMe	3-OEt	4-OMe
Et	H	Br	NHMe	3-OEt	4-OMe
i-Pr	H	Cℓ	NHMe	3-OEt	4-OMe
i-Pr	H	Br	NHMe	3-OEt	4-OMe
Et	H	Cℓ	NHEt	3-OEt	4-OMe
Et	H	Br	NHEt	3-OEt	4-OMe
Et	H	Cℓ	NHMe	3-O-n-Pr	4-OMe
Et	H	Br	NHMe	3-O-n-Pr	4-OMe

R_1	R_2	X	Y	Z_1	Z_2
H	H	Cℓ	O-sec-Bu	3-O$(CH_2)_2$Ph	4-OMe
H	H	Br	O-sec-Bu	3-O$(CH_2)_2$Ph	4-OMe
H	H	Br	OCHMePh	3-OMe	4-OMe
H	H	Br	OCHMePh	3-OEt	4-OMe
H	H	Cℓ	OCHMePh	3-O-n-Bu	4-OMe
H	H	Br	OCHMePh	3-O-n-Bu	4-OMe
H	H	Cℓ	OCHMePh	3-O$(CH_2)_2$Ph	4-OMe
H	H	Br	OCHMePh	3-O$(CH_2)_2$Ph	4-OMe
H	H	Cℓ	OCHEtPh	3-OMe	4-OMe
H	H	Br	OCHEtPh	3-OMe	4-OMe
H	H	Cℓ	O~	3-OMe	4-OMe
H	H	Br	O~	3-OMe	4-OMe
H	H	Cℓ	O~Me	3-OMe	4-OMe
H	H	Br	O~Me	3-OMe	4-OMe
H	H	Cℓ	OCH(Me)~	3-OMe	4-OMe
H	H	Br	OCH(Me)~	3-OMe	4-OMe
H	H	Cℓ	OCH(Me)CH_2-≡	3-OMe	4-OMe
H	H	Br	OCH(Me)CH_2-≡	3-OMe	4-OMe

As the manner of administration of the compounds of the present invention, there may be mentined a non-oral administration by injection (subcutaneous, intravenous, intramuscular or intraperitoneal injection), an ointment, a suppository or an aerosol, or an oral administration in the form of tablets, capsules, granules, pills, sirups, liquids, emulsions or suspensions.

The above pharmacological or veterinary composition contains a compound of the present invention in an amount of from about 0.1 to about 99.5% by weight, preferably from about 0.5 to about 95% by weight, based on the total weight of the composition. To the compound of the present invention or to the composition containing the compound of the present invention, other pharmacologically or veterinarily active compounds may be incorporated. Further, the composition of the present invention may contain a plurality of compounds of the present invention.

The clinical dose of the compound of the present invention varies depending upon the age, the body weight, the sensitivity or the symptom, etc. of the patient. However, the effective daily dose is usually from 0.003 to 1.5 g, preferably from 0.01 to 0.6 g, for an adult. However, if necessary, an amount outside the above range may be employed.

The compounds of the present invention may be formulated into various suitable formulations depending upon the manner of administration, in accordance with conventional methods commonly employed for the preparation of pharmaceutical formulations.

Namely, tablets, capsules, granules or pills for oral administration, may be prepared by using an excipient

such as sugar, lactose, glucose, starch or mannitol; a binder such as sirups, gum arabic, gelatin, sorbitol, tragacant gum, methyl cellulose or polyvinylpyrrolidone; a disintegrant such as starch, carboxymethyl cellulose or its calcium salt, crystal cellulose powder or polyethylene glycol; a glass agent such as talc, magnesium or calcium stearate or colloidal silica; or a lubricant such as sodium laurate or glycerol. The injections, solutions, emulsions, suspensions, sirups or aerosols, may be prepared by using a solvent for the active ingredient such as water, ethyl alcohol, isopropyl alcohol, propylene glycol, 1,3-butylene glycol, or polyethylene glycol; a surfactant such as a sorbitol fatty acid ester, a polyoxyethylene sorbitol fatty acid ester, a polyoxyethylene fatty acid ester, a polyoxyethylene ether of hydrogenated caster oil or lecithin; a suspending agent such as a sodium salt of carboxymethyl, a cellulose derivative such as methyl cellulose, or a natural rubber such as tragacant gum or gum arabic; or a preservative such as a paraoxy benzoic acid ester, benzalkonium chloride or a salt of sorbic acid. Likewise, the suppositories may be prepared by using e.g. polyethylene glycol, lanolin or cocoa butter.

TEST EXAMPLES

A. Antagonistic activity test against SRS-A

SRS-A is a mixture of leukotriene C_4 (hereinafter referred to as LTC_4), leukotriene D_4 (hereinafter referred to as LTD_4), leukotriene E_4 (hereinafter referred to as LTE_4) and the like. Accordingly, antagonistic activities against SRS-A can be evaluated by one of the following two test methods:

(1) A method of examining the antagonistic activities against SRS-A obtained from a sensitized guinea-pig,

(2) A method of examining the antagonistic activities against LTC_4, LTD_4 or LTE_4.

The present inventors examined the antagonistic activities of compounds of the formula I against SRS-A by using the following test methods.

1) Test methods

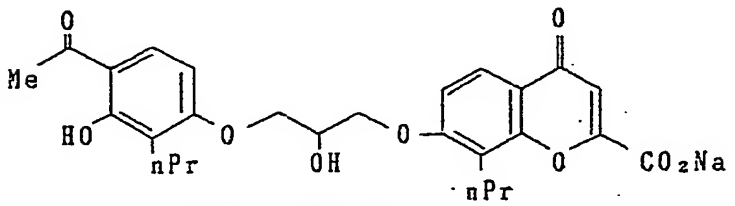
(1) in vitro test

LTD_4 antagonism in guinea-pig trachea

Antagonism for LTD_4 was determined in isolated male guinea-pig (300 - 400 g) trachea prepared as spiral strip. Tracheal preparations were suspended under 1 g tension in 10 ml organ baths containing 5 μM of indomethacin and they were incubated for 1 hr prior to use. Contractile responses to LTD_4 (2×10^{-8} g/ml) were obtained after the maximal response to histamine (10^{-4} M). Test compounds dissolved in 100% dimethyl sulfoxide were added to the organ baths (final concentration of 10^{-6} g/ml or 10^{-7} g/ml) 30 min prior to LTD_4 addition, and then contractile responses to LTD_4 were compared with those of control which was obtained from a paired trachea in the absence of test compounds. LTD_4-induced contractions were expressed as a percentage of the maximal response to histamine. The antagonism was determined as follows:

Antagonism (%) = (1.0 - % contraction in test/% contraction in control) × 100

FPL-55712 (Fisons Limited) approved as a selective SRS-A antagonist, was used as the control.



F P L − 55712

(2) In vivo test

Effect on anaphylactic bronchoconstriction mediated by endogeneously liberated SRS-A in passively sensitized guinea-pig

Male guinea-pigs (350 - 450 g) were passively sensitized with intravenous (I.v.) injection of 0.125 ml rabbit anti-EA (egg albumin) serum (Capple Laboratories) 1 to 2 days preceding the experiment. Antigen-induced anaphylactic bronchoconstrictions mediated by endogeneously liberated SRS-A were measured by modified method of Konzett and Rossler (Arch. Exp. Path. Pharmak., 195, 71, 1940). Sensitized guinea-pigs were anaesthetized with intraperitoneal injection of urethane (1.5 g/kg). The right jugular vein was cannulated for the administration of the all agents and trachea was cannulated to record total pulmonary resistance. Guinea-pigs were artificially ventilated by a small animal respirator (Shinano, Model SN-480-7) set at a stroke

volume of 4.5 ml and a rate of 50 breaths per min. The change in pulmonary resistance was measured with a pressure transducer (Nihon Kohden, Model TP-602T) connected to a T-tube on the tracheal cannula. The increase in air overflow volume was expressed as a percentage of the maximum bronchoconstriction obtained by clamping off the trachea. Following surgical preparation, the animals were pretreated with indomethacin (2 mg/kg, 10 min), pyrilamine (2 mg/kg, 6 min) and propranolol (0.1 mg/kg, 5 min) prior to the EA challenge (0.2 mg/kg). All test compounds were administered orally 2 hrs before the EA challenge. Inhibition (%) of bronchoconstriction was determined as follows: Inhibition (%) = (1.0 - % maximum bronchoconstriction in test/% maximum bronchoconstriction in control) × 100. The maximum bronchoconstriction was 62 ± 6% (Mean ± S.E.M; n = 6) and the number of test animals was 5 - 6.

2) Test Results

(1) in vitro test

LTD_4 antagonisms by test compounds at a concentration of 10^{-6} g/ml are shown in Table 2. In parenthesis in Table 2, LTD_4 antagonisms by test compounds at a concentration of 10^{-7} g/ml are shown.

Table 2

Test compound No.	Antagonism (%)	Test compound No.	Antagonism (%)
5	54	64	90
7	50	65	96
10	66	66	100(48)
22	59	67	100(82)
23	51	68	92
27	72	69	100(83)
30	38	70	66
33	93	71	66
36	70	72	75
45	50	73	100
46	73	74	100
47	79	75	77
48	99	77	50
50	95	78	56
51	94	79	79
52	100	80	100
53	100	84	59
54	95	85	85
55	81	86	100(48)
56	100(51)	89	96(55)
57	100(37)	90	96(70)
58	100(40)	91	100(76)
60	100(38)	92	63
61	96	94	68
63	92	FPL-55712	94(48)

(2) in vivo test

Each of test compounds No. 68 and No. 69 as representative compounds of the present invention showed significant inhibitory effects over the control at a dose by oral administration as identified in Table 3 ($P < 0.05$). The results are shown in Table 3.

Table 3

Test compound No.	Dose (mg/kg)	Inhibition (%)
68	30	51
	10	63
69	30	52

B. Acute toxicity test

The lethal ratio was determined in CD-1(ICR) strain male mice (5 weeks old) at 7 days after the oral administration of test compounds. The results are shown in Table 4.

Table 4

Test compound No.	Dose (mg/kg)	Lethal ratio Death number/Experimental number
68	1200	0 / 5
69	1200	0 / 5

From these results, it is evident that the compounds of the present invention exhibit prominent antagonistic activities against SRS-A and its major constituents peptide leukotrienes in vitro and in vivo. Further, the compounds of the present invention show strong pharmacological activities and low toxicity even by oral administration. Therefore, the compounds of the present invention are expected to be useful as prophylactic and therapeutic drugs against various immediate type allergic diseases such as bronchial asthma, allergic rhinitics, urticaria and hay fever, various inflamatory diseases such as rheumatoid arthritis and spondyloarthritis, or ischemic heart diseases such as angina pectoris and myocardial infarction, induced by SRS-A or by one of leukotriene C_4, D_4 and E_4 as its constituents or a mixture thereof.

Now, the present invention will be described in detail with reference to Examples including Reference Examples and Formulation Examples. However, it should be understood that the present invention is by no means restricted by these specific Examples. In specific Examples, in Reference Examples, or in Table 5, the symbols "NMR", "IR" and "MS" indicate "nuclear magnetic resonance spectrum", "infrared spectrum" and "mass spectrometry", respectively. IR was measured by the potassium bromide disk method and NMR was measured in heavy chloroform, unless otherwise specified. In the MS data, only the principal peaks or typical fragment peaks are given.

REFERENCE EXAMPLE 1

2-ethyl-4,5-dichloro-6-hydroxy-3(2H)pyridazinone

A mixture comprising 5.00 g of 3,6-dihydroxy-4,5-dichloropyridazine, 2.21 g of sodium hydroxide, 5.60 g of ethyl iodide, 40 ml of ethanol and water, was stirred at a temperature of from 60 to 70°C for 4 hours. Most ethanol was distilled off under reduced pressure. Then, dilute hydrochrolic acid and chloroform were added to the residue, and the mixture was vigorously shaked. The chloroform layer was separated and washed with water, followed by drying over sodium sulfate. Then, the solvent was distilled off to obtain a light orange solid substance. The solid substance was treated with benzene to obtain 3.56 g of the above identified compound as colorless crystals.

NMR ($CDC\ell_3$ + DMSO-d_6) δ : 4.05(2H, q), 1.33(3H, t).
IR (νmax cm^{-1}) : 3150, 1635, 1620, 1560, 1510,
MS (m/e) : 208(M+), 193, 180(100%), 166, 148.

REFERENCE EXAMPLE 2

4,5-dichloro-6-ethoxy-3(2H)pyridazinone

27.15 g of 3,6-dihydroxy-4,5-dichloropyridazine was dissolved in a solution prepared by dissolving 6.43 g of sodium hydroxide in 200 ml of water, and the solution was subjected to freeze-drying to obtain 32.80 g of sodium salt of 3,6-dihydroxy-4,5-dichloropyridazine as a light yellow powder. A mixture comprising 14.21 g of the sodium salt, 13.10 g of ethyl iodide and 200 ml of N,N-dimethylformamide was stirred at a temperature of from 70 to 80° C for 4 hours. The solvent was distilled off under reduced pressure, and water was added to the residue thereby obtained. The mixture was extracted with chloroform. The extract was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off to obtain a light orange solid substance. The solid substance was washed with 250 ml of a solvent mixture of benzene-ethyl acetate (3 : 1 v/v) to obtain 2.83 g of the above identified compound having a melting point of from 212 to 212.5°C as colorless crystals. The residual washing solvent was treated with 10 g of silica gel, and then the solvent was distilled off to obtain a light yellow solid substance. The solid substance was washed with diethyl ether to obtain additional 2.37 g of the above identified compound. (Total yield: 5.20 g)

NMR ($CDC\ell_3$ + DMSO-d_6) : 4.20(2H, q), 1.38(3H, t).
IR (νmax cm^{-1}) : 2975, 2850, 1645, 1585, 1380. MS (m/e) : 208(M+), 180(100%), 150.

In the same manner as above, by using isopropyl iodide, benzyl bromide and α-phenylethyl bromide instead of ethyl iodide, 4,5-dichloro-6-i-propoxy-3(2H)pyridazinone having a melting point of from 210 to 211°C, 4,5-dichloro-6-benzyloxy-3(2H)pyridazinone having a melting point of from 111 to 113°C and 4,5-dichloro-6-(α-methylbenzyloxy)-3(2H)pyridazinone having a melting point of from 160 to 161°C were prepared, respectively.

REFERENCE EXAMPLE 3

2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone

587 mg of trimethysilylethoxymethyl chloride was added to a mixture comprising 500 mg of 4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 17), 911 mg of di-i-propylethylamine and 15 ml of dichloromethane, and the mixture was stirred at room temperature for 10 minutes. The solvent was distilled off and the residue thereby obtained was extracted with chloroform. The extract was washed twice with a saturated copper sulfate solution and once with water in this order and dried over sodium sulfate. Then, the solvent was distilled off to obtain a yellow oily substance. The oily substance was purified by silica gel thin layer chromatography by using diethyl ether as the developper, to obtain 600 mg of the above identified compound as a yellow oily substance. This oily substance was allowed to stand to gradually change to crystals having a melting point of from 56 to 57.5°C.

NMR δ : 6.85(3H, s), 6.69(1H, m), 5.48(2H, s), 4.78, 4.68(2H, d), 4.10(2H, q), 3.88(3H, s), 3.80(2H, t), 1.49(3H, t), 1.00(3H, t), 0.0(9H, s).
MS (m/e) : 484(M+), 483(100%), 353, 319

In the same manner as above, 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3,4-dimethoxybenzylamino)-6-nitro-3(2H)pyridazinone (yellow oily substance) was prepared from 4-chloro-5-(3,4-dimethoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 87).

REFERENCE EXAMPLE 4

2-(2-trimethylsilylethoxymethy)-4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-6-methoxy-3(2H)pyridazinone

A mixture comprising 250 mg of 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone prepared in Reference Example 3, 42 mg of sodium methoxide and methanol, was stirred at room temperature for 10 minutes. Water was added to the reaction mixture and the solvent was distilled off, and the residue thereby obtained was extracted with chloroform. The extract was washed with water and dried over sodium sulfate. Then, the solvent was distilled off to obtain a yellow oily substance. The oily substance was purified by silica gel thin layer chromatography by using diethyl ether as the

developer, to obtain 220 mg of the above identified compound as a light yellow oily substance.

NMR δ : 6.78(3H, s), 5.30(2H, s), 5.10(1H, m), 4.82, 4.74(2H, d), 4.10(2H, q), 3.85(6H, s), 3.72(2H, t), 1.48(3H, t), 1.00(3H, t), 0.0(9H, s).

MS (m/e) : 469(M+), 468(100%), 304, 188

In the same manner as above, by using sec-butoxide instead of sodium methoxide, 2-(2-trimethylsilylethoxymethy)-4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-6-sec-butoxy-3(2H)pyridazinone (oily substance) and 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3,4-dimethoxybenzylamino)-6-sec-butoxy-3(2H)pyridazinone (oily substance), were prepared from the corresponding 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3-alkoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinones.

REFERENCE EXAMPLE 5

2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3,4-dimethoxybenzylamino)-6-n-propylmercapto-3(2H)pyridazinone

A solution prepared by dissolving 916 mg of 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3,4-dimethoxybenzylamino)-6-nitro-3(2H)pyridazinone prepared in Reference Example 4 in 2 ml of toluene, was dropwise added under cooling with ice and stirring to a mixture comprising of 1 ml of n-propyl mercaptan, 166 mg of sodium amide and 6 ml of toluene. After dropwise addition, the reaction mixture was stirred at the same temperature for further 20 minutes. A saturated ammonium chloride aqueous solution was added to the reaction mixture, and the mixture was extracted with chloroform. The extract was washed with water and dried over sodium sulfate. Then, the solvent was distilled off and the residue thereby obtained was purified by silica gel column chromatography by using benzene-ethyl acetate (12 : 1 v/v) as the eluent, to obtain 500 mg of the above identified compound as a light yellow oily susbtance.

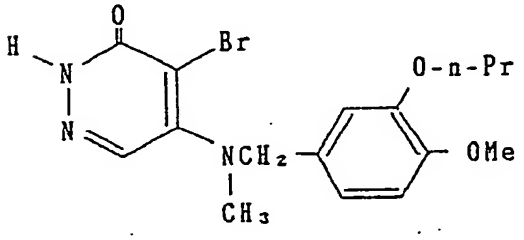
NMR δ : 6.72(3H, s), 5.33(2H, s), 5.0 - 4.6(3H, m), 3.81(6H, s), 3.67(2H, t), 2.08(2H, t), 1.9 - 0.8(7H, m), 0.00(9H, s)

MS (m/e) : 499(M+), 456, 398, 383, 164, 151(100%).

In the same manner as above, by using i-propyl mercaptan, i-buthyl mercaptan and sec-buthyl mercaptan instead of n-propyl mercaptan, the respective 6-alkylmercapto forms i.e. 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3,4-dimethoxybenzylamino)-6-i-propylmercapto, -6-i-butylmercapto and -6-sec-butylmercapto-3(2H)pyridazinones (each being a light yellow oily substance), were prepared.

EXAMPLE 1

4-bromo-5-(3-n-propoxy-4-methoxy-N-methylbenzylamino)-3(2H)pyridazinone (Compound No. 6)



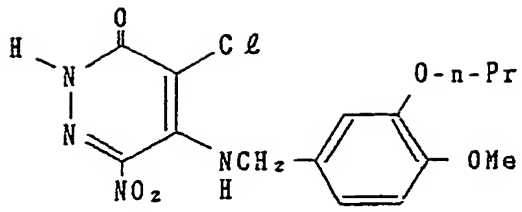
A mixture comprising 300 mg of 4,5-dibromo-3(2H)pyridazinone, 740 mg of 3-n-propoxy-4-methoxy-N-methylbenzylamine and 10 ml of ethanol, was refluxed under stirring for 7 hours. Then, ethanol was distilled off under reduced pressure, dilute hydrochloric acid was added to the residue thereby obtained, and the mixture was extracted with ethyl acetate. The extract was washed twice with water and dried over sodium sulfate. Then, the solvent was distilled off to obtain a yellow solid substance. The product was crystallized from ethyl acetate, to obtain 310 mg of the above identified compound having a melting point of from 149 to 150°C as light yellow crystals.

NMR δ : 7.53(1H, s), 6.75(3H, s), 4.53(2H, s), 3.91(2H, t), 3.81(3H, s), 3.01(3H, s), 1.84(2H, hexalet), 1.01(3H, t).

MS (m/e) : 302(M+-Br,100%), 179, 137.

EXAMPLE 2

4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 22)



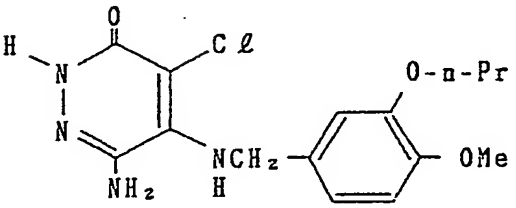
A mixture comprising 8.0 g of 4,5-dichloro-6-nitro-3(2H)pyridazinone, 29.75 g of 3-n-propoxy-4-methoxybenzylamine and 160 ml of ethanol, was refluxed under stirring for 15 hours. Ethanol was distilled off under reduced pressure, and water was added to the residue thereby obtained. The mixture was extracted with chloroform. The extract was washed with water and dried over sodium sulfate. Then, the solvent was distilled off to obtain an orange solid substance. This product was crystallized from a solvent mixture of methanol-water, to obtain 6.50 g of the above identified compound having a melting point of from 169 to 171°C as orange crystals.

NMR ($CDC\ell_3$ + DMSO-d_6) δ : 7.01(1H, t), 6.77 (3H, s), 4.62(2H, d), 3.90(2H, t), 3.77(3H, s), 1.78(2H, hexalet), 1.00(3H, t).

MS (m/e) : 368(M+), 333, 179(100%), 137.

EXAMPLE 3

4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-amino-3(2H)pyridazinone (Compound No. 23)

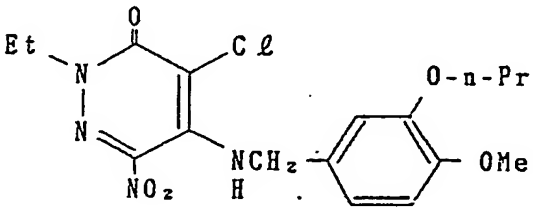


1.00 g of 4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 22) prepared in Example 2, was dissolved in a solvent mixture of 20 ml of ethanol and 20 ml of a 10% sodium carbonate aqueous solution, 3.30 g of sodium hydrosulfite was gradually added thereto at room temperature under stirring. The mixture was stirred at room temperature for 1 hour, and was neutralized with glacial acetic acid. Then, ethanol was distilled off under reduced pressure, and water was added to the residue thereby obtained. The mixture was extracted with chloroform. The extract was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off to obtain light yellow crystals. This product was crystallized from a solvent mixture of methanol-diethyl ether, to obtain 634 mg of the above identified compound having a melting point of from 187.5 to 189.5°C as colorless crystals.

MS (m/e) : 338(M+), 303, 179(100%), 137.

EXAMPLE 4

2-ethyl-4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 24)



A mixture comprising 500 mg of 4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 22) prepared in Example 2, 634 mg of ethyl iodide, 562 mg of anhydrous potassium

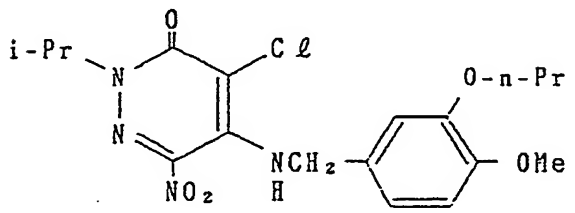
carbonate and 25 ml of methyl ethyl ketone, was refluxed under stirring for 1.5 hours. The solvent was distilled off under reduced pressure, and water was added to the residue thereby obtained and the mixture was extracted with diethyl ether. The extract was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off, and the residual oily substance thereby obtained was crystallized from a solvent mixture of diethyl ether-n-hexane, to obtain 473 mg of the above identified compound having a melting point of from 76 to 77°C as yellow crystals.

NMR δ : 6.79(3H, s), 6.60(1H, broad t), 4.68(2H, d), 4.30(2H, q), 3.93(2H, t), 3.82(3H, s), 1.84(2H, hexalet), 1.39(3H, t), 1.03(3H, t).

MS (m/e) : 396(M+), 361, 179(100%), 137.

EXAMPLE 5

2-i-propyl-4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 25)



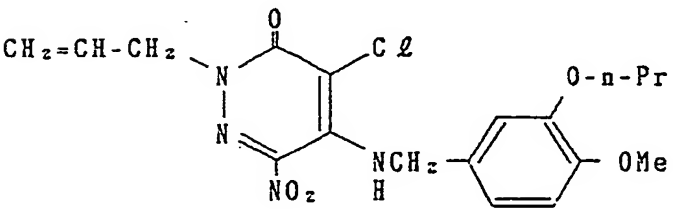
A mixture comprising 500 mg of 4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 22) prepared in Example 2, 691 mg of isopropyl iodide, 562 mg of anhydrous potassium carbonate and 25 ml of methyl ethyl ketone, was refluxed under stirring for 1.5 hours. The solvent was distilled off under reduced pressure, and water was added to the residue thereby obtained. The mixture was extracted with diethyl ether. The extract was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off. The residual oily substance thereby obtained was crystallized from a solvent mixture of diethyl ether-n-hexane, to obtain 435 mg of the above identified compound having a melting point of from 82.5 to 84°C as yellow crystals.

NMR δ : 6.80(3H, s), 6.63(1H, broad t), 5.25 (1H, heptalet), 4.69(2H, d), 3.94(2H, t), 3.83(3H, s), 1.85(2H, hexalet), 1.38(6H, d), 1.04(3H, t).

MS (m/e) : 410(M+), 375, 179(100%), 137.

EXAMPLE 6

2-(2-propenyl)-4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Comound No. 26)



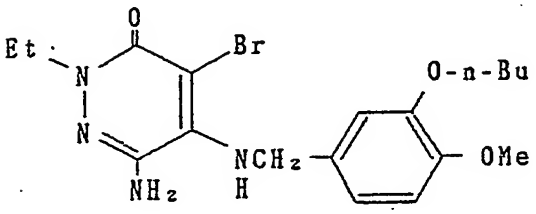
A mixture comprising 500 mg of 4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 22) prepared in Example 2, 820 mg of allyl bromide, 937 mg of anhydrous potassium carbonate and 25 ml of methyl ethyl ketone, was refluxed under stirring for 1.5 hours. The solvent was distilled off under reduced pressure, water was added to the residue thereby obtained, the mixture was extracted with diethyl ether. The extract was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off, and the residue was purified by silica gel column chromatography by using a solvent mixture of benzene: ethyl acetate (85 : 15 v/v) as the eluent, to obtain 394 mg of the above identified compound having a melting point of from 62.5 to 64°C as yellow crystals.

NMR δ : 6.81(3H, s), 6.59(1H, broad t), 6.1 - 4.4(7H, m), 3.95(2H, t), 3.85(3H, s), 1.84(2H, hexalet), 1.02(3H, t).

MS (m/e) : 408(M+), 373, 179(100%), 137.

EXAMPLE 7

2-ethyl-4-bromo-5-(3-n-butoxy-4-methoxybenzylamino)-6-amino-3(2H)pyridazinone (Compound No. 32)



A mixture comprising 280 mg of 4-bromo-5-(3-n-butoxy-4-methoxybenzylamino)-6-amino-3(2H)pyridazinone (Compound No. 30) prepared according to the process of Example 3 from 4-bromo-5-(3-n-butoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 29) as the starting material, 0.29 ml of ethyl iodide, 487 mg of anhydrous potassium carbonate and 15 ml of methyl ethyl ketone, was refluxed under stirring for 2 hours. The solvent was distilled off under reduced pressure, and water was added to the residue thereby obtained. The mixture was extracted with chloroform. The extract was washed with a saturated sodium chloride aqueous solution and dried over sodium sulfate. Then, the solvent was distilled off, the residue thereby obtained was subjected to silica gel thin layer chromatography by using a solvent mixture of chloroform : methanol (9 : 1 v/v) as the developer, the oily substance thereby obtained was crystallized from a solvent mixture of diethyl ether-n-hexane, to obtain 180 mg of the above identified compound having a melting point of from 108 to 110.5°C as light yellow crystals.

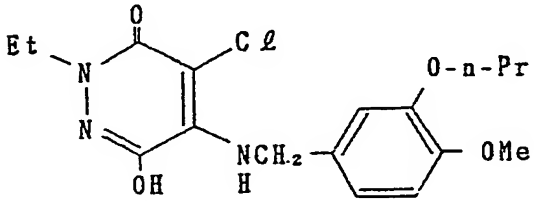
NMR δ : 6.78(3H, s), 5.1 - 3.8(9H, m), 3.80 (3H, s), 2.0 - 1.4(4H, m), 1.25, 0.95(each 3H,t).

MS (m/e) : 424(M+), 345, 193(100%), 137.

Further, the above identified compound was prepared also by subjecting 2-ethyl-4-bromo-5-(3-n-butoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 31) to the same reduction as in Example 3.

EXAMPLE 8

2-ethyl-4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-hydroxy-3(2H)pyridazinone (Compound No. 43)



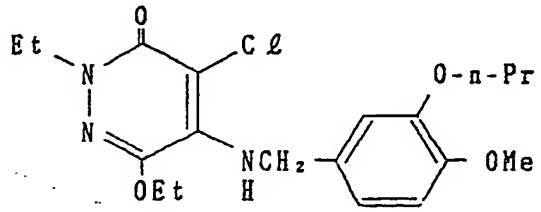
A mixture comprising 523 mg of 2-ethyl-4,5-dichloro-6-hydroxy-3(2H)pyridazinone prepared in Reference Example 1, 1.71 g of 3-n-propoxy-4-methoxybenzylamine, 15 ml of 1,4-dioxane and 15 ml of water, was refluxed under stirring for 24 hours, and 1.71 g of 3-n-propoxy-4-methoxybenzylamine was further added thereto, and the reaction was conducted under the same condition for 2 days. The solvent was distilled off under reduced pressure, and dilute hydrochloric acid was added to the residue thereby obtained. The mixture was extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution in this order, and dried over sodium sulfate. Then, the solvent was distilled off to obtain a yellow oily substance. The oily substance was purified by silica gel column chromatography, and the slightly yellow oily substance obtained by eluting with a solvent mixture of benzene-ethyl acetate (1 : 2 v/v) was crystallized from ethyl acetate-diethyl ether, to obtain 418 mg of the above identified compound having a melting point of from 73 to 74°C as colorless crystals.

NMR δ : 7.79(1H, broad s), 6.79(3H, s), 5.4 - 5.0(1H, m), 6.9 - 6.4(2H, m), 3.92(2H, t), 3.81(3H, s), 1.82(2H, hexalet), 1.17, 1.01(each 3H,t).

MS (m/e) : 367(M+), 332, 179(100%), 137.

EXAMPLE 9

2-ethyl-4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-ethoxy-3(2H)pyridazinone (Compound No. 50)



(1) A mixture comprising 184 mg of 2-ethyl-4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-hydroxy-3(2H)pyridazinone (Compound No. 43) prepared in Example 8, 156 mg of ethyl iodide, 207 mg of anhydrous potassium carbonate and 15 ml of methyl ethyl ketone, was refluxed under stirring for 2 hours. The solvent was distilled off under reduced pressure, and water was added to the residue thereby obtained and the mixture was extracted with ethyl acetate. The extract was washed with water and a saturated sodium chloride aqueous solution in this order and dried over sodium sulfate. Then, the solvent was distilled off to obtain a slightly yellow viscous oily substance. The oily substance was crystallized from diethyl ether-n-hexane, to obtain 158 mg of the above identified compound having a melting point of from 77.5 to 78°C as colorless crystals.

NMR δ : 6.75(3H, s), 5.0 - 4.6(3H, m), 4.60, 4.40(each 2H, q), 3.93(2H, t), 3.81(3H, s), 1.84(2H, hexalet), 1.35, 1.29, 1.04(each 3H, t).

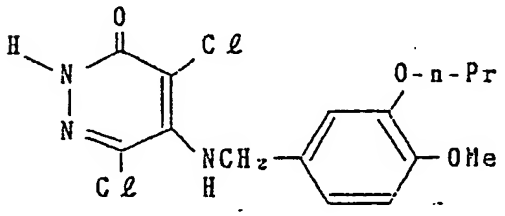
IR (νmax cm^{-1}) : 3280, 1625, 1605, 1530.

MS (m/e) : 395(M+), 360, 179(100%), 137.

(2) 300 mg of 2-ethyl-4-chloro-5-(3-n-propoxy-4-methoxybenzylamino)-6-nitro-3(2H)pyridazinone (Compound No. 24) prepared in Example 4, was dissolved in 6 ml of dried ethanol, and 160 mg of sodium ethoxide was added thereto. The mixture was gently refluxed under stirring for 10 minutes. After cooling, ice water was poured into the reaction solution, and then most ethanol was distilled off under reduced pressure. The residue was extracted with ethyl acetate. The extract was washed with 1N hydrochloric acid, water and a saturated sodium chloride aqueous solution in this order and dried over sodium sulfate. The solvent was distilled off and the residual oily substance thereby obtained was purified by silica gel thin layer chromatography by using benzene : ethyl acetate (7 : 3 v/v) as the developer, to obtain 300 mg of the above identified compound. The physical properties and the spectrum data of NMR, IR and MS of the compound completely agreed to those of the compound prepared by the above method (1).

EXAMPLE 10

4,6-dichloro-5-(3-n-propoxy-4-methoxybenzylamino)-3(2H)pyridazinone (Compound No. 71)



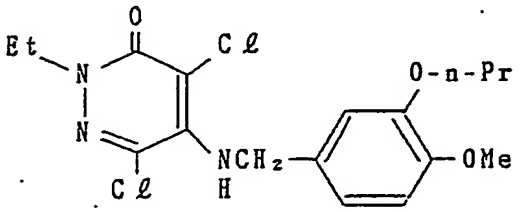
A mixture comprising 997 mg of 4,5,6-trichloro-3(2H)pyridazinone, 3.20 g of 3-n-propoxy-4-methoxybenzylamine and 30 ml of ethanol, was refluxed under stirring for 2 hours. Ethanol was distilled off under reduced pressure, and dilute hydrochloric acid was poured into the residue thereby obtained. The mixture was extracted with ethyl acetate. The extract was washed with water and dried over sodium sulfate. Then, the solvent was distilled off to obtain a light brown viscous oily substance. The residue was subjected to silica gel column chromatography, and the second fraction obtained by eluting with a solvent mixture of benzene-ethyl acetate (2.5 : 1 v.v) was separated to obtain a colorless solid substance. The product was crystallized from a solvent solution of methanol-diethyl ether, to obtain 513 mg of the above identified compound having a melting point of from 181 to 183°C as colorless crystals.

NMR ($CDCl_3$ + DMSO-d_6) δ : 12.72 (1H, broad s), 6.79 (3H, s), 6.0 - 5.6(1H, m), 4.78(2H, d), 3.91(2H, t), 3.79(3H, s), 1.80(2H, hexalet), 1.02(3H, t).

MS (m/e) : 357(M+), 322, 179(100%), 137.

EXAMPLE 11

2-ethyl-4,6-dichloro-5-(3-n-propoxy-4-methoxybenzylamino)-3(2H)pyridazinone (Compound No. 62)



(1) A mixture comprising 150 mg of 4,6-dichloro-5-(3-n-propoxy-4-methoxybenzylamino)-3(2H)pyridazinone (Compound No. 71) prepared in Example 10, 0.2 ml of ethyl iodide, 116 mg of anhydrous potassium carbonate and 10 ml of methyl ethyl ketone, was refluxed under stirring for 1 hour. The reaction mixture was subjected to distillation under reduced pressure, and water was poured into the residue thereby obtained. The mixture was extracted with ethyl acetate. The extract was washed with water and dried over sodium sulfate. Then, the solvent was distilled off to obtain a light yellow viscous oily substance. The product was crystallized from a solvent mixture of diethyl ether-n-hexane, to obtain 139 mg of the above identified compound having a melting point of from 101 to 103°C as colorless crystals.

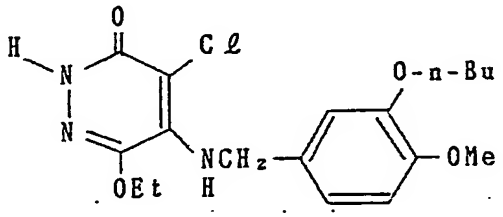
NMR δ : 6.83(3H, s), 4.80(3H, broad s), 4.12(2H, q), 3.96(2H, t), 3.84(3H, s), 1.86(2H, hexalet), 1.34, 1.05(each 3H, t).

MS (m/e) : 385(M+), 350, 179(100%), 137.

(2) A mixture comprising 455 mg of 2-ethyl-4,5,6-trichloro-3(2H)pyridazinone, 1.20 g of 3-n-propoxy-4-methoxybenzylamine and 20 ml of ethanol, was refluxed under stirring for 3.5 hours. Ethanol was distilled off under reduced pressure, and water was poured into the residue thereby obtained. The mixture was extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid and water in this order and dried over sodium sulfate. Then, the solvent was distilled off to obtain a light brown viscous oily substance. The product was purified by silica gel column chromatography by using a solvent mixture of benzene-ethyl acetate (15 : 1 v/v) as the eluent, to obtain 277 mg of the above identified compound. The physical properties and the spectrum data of NMR and MS of the compound completely agreed to those of the compound prepared by the method (1).

EXAMPLE 12

4-chloro-5-(3-n-butoxy-4-methoxybenzylamino)-6-ethoxy-3(2H)pyridazinone (Compound No. 68)



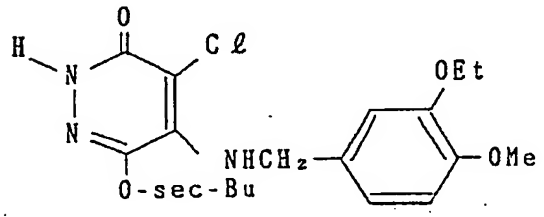
A mixture comprising 7.32 g of 4,5-dichloro-6-ethoxy-3(2H)pyridazinone prepared in Reference Example 2, 21.95 g of 3-n-butoxy-4- methoxybenzylamine, 60 ml of 1,4-dioxane and 60 ml of water, was refluxed under stirring for 15 hours. Then, most 1,4-dioxane was distilled off under reduced pressure, and dilute hydrochloric acid was added for acidification. Then, chloroform was added thereto, and the mixture was vigorously shaked. The precipitated crystals were separated by filtration, and the chloroform layer of the filtrate was subjected to liquid separation and washed with water and dried over sodium sulfate. Then, the solvent was distilled off to obtain a light yellow oily substance. The product was crystallized from n-propanol-di-i-propyl ether (1 : 9 v/v), to obtain 10.48 g of the above identified compound having a melting point of from 117 to 118°C as colorless crystals.

NMR δ : 11/79 (1H, broad s), 6.76(3H, s), 5.2 - 4.8 (1H, m), 4.80, 4.71(2H, d), 4.19(2H, q), 3.96(2H, t), 3.81(3H, s), 2.1 - 1.3(4H, m), 1.32, 0.97(each 3H, t).

MS (m/e) : 381(M+), 346, 193(100%), 137.

EXAMPLE 13

4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-6-sec-butoxy-3(2H)pyridazinone (Compound No. 88)



A mixture comprising 150 mg of 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3-ethoxy-4-methoxybenzylamino)-6-sec-butoxy-3(2H)pyridazinone prepared in Reference Example 4, 1.46 ml of tetra-n-butylammonium fluoride (1M tetrahydrofuran solution) and 5 ml of 1,2-dimethoxyethane, was refluxed under stirring for 3 hours. The solvent was distilled off under reduced pressure, and the residue thereby obtained was extracted with chloroform. The extract was washed twice with 1N hydrochloric acid and once with water in this order and dried over sodium sulfate. Then, the solvent was distilled off to obtain a dark brown oily substance. The oily substance was purified by silica gel preparative thin layer chromatography by using ethyl acetate as the developer, to obtain a light yellow solid substance. The product was crystallized from chloroform-diethyl ether, to obtain 50 mg of the above identified compound having a melting point of from 130.5 to 132°C as slightly yellow crystals.

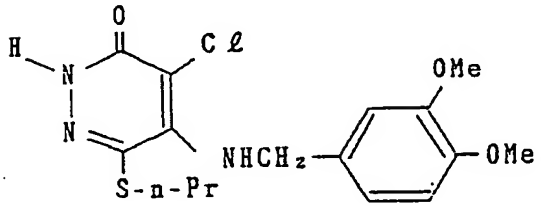
NMR ($CDC\ell_3$ + DMSO-d_6)

δ : 11.70(1H, s), 6.70(3H, s), 5.02(2H, m), 4.81, 4.74 (2H, d), 4.05(2H, q), 3.82(3H, s), 1.50(9H,m), 1.00(2H, m).

MS (m/e) : 381(M+), 346, 165(100%).

EXAMPLE 14

4-chloro-5-(3,4-dimethoxybenzylamino)-6-n-propylmercapto-3(2H)pyridazinone (Compound No. 92)



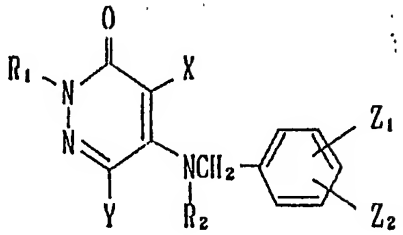
A mixture comprising 256 mg of 2-(2-trimethylsilylethoxymethyl)-4-chloro-5-(3,4-dimethoxybenzylamino)-6-n-propylmercapto-3(2H)pyridazinone prepared in Reference Example 5, 3 ml of tetra-n-butylammonium fluoride (1M tetrahydrofuran solution) and 1.5 ml of N,N-dimethylformamide, was stirred at a temperature of 150°C for 3 hours. A 1N hydrochloric acid aqueous solution was added to the reaction mixture, and the mixture was extracted with chloroform. The extract was washed with water and a sodium hydrogencarbonate aqueous solution in this order, and dried over sodium sulfate. The solvent was distilled off and the residue thereby obtained was purified by silica gel thin layer chromatography by using benzene-ethyl acetate (1 : 1 v/v) as the developer, to obtain 39 mg of the above identified compound as a light yellow solid substance. The product was changed into slightly yellow crystals having a melting point of from 129 to 130°C by the recrystallization thereof from a solvent mixture of ethyl acetate-diethyl ether-n-hexane.

NMR δ : 6.73(3H, s), 5.1 - 4.4(3H, m), 3.81(6H, s), 2.97(2H, t), 2.1 - 1.4(2H, m), 0.98(3H, t).

MS (m/e) : 369(M+), 334, 165, 151(100%).

The compounds prepared in the same manner as in Examples are shown in Table 5. The Example No. in the right hand side column is the number of the Example in accordance with which the particular compound was prepared.

Table 5



Compound No.	R_1	R_2	X	Y	Z_1	Z_2	Melting point (°C)	MS(m/e)	Example No.
1	H	Me	Cℓ	H	3-OMe	4-OMe	169~178	309(M^+), 151(100%)	1
2	H	Me	Br	H	3-OMe	4-OMe	160~165.5	274(M^+-Br), 151(100%)	1
3	H	Me	Cℓ	H	3-OEt	4-OMe	161~162	323(M^+), 165(100%)	1
4	H	Me	Br	H	3-OEt	4-OMe	166~167	288(M^+-Br,100%), 165	1
5	H	Me	Cℓ	H	3-O-n-Pr	4-OMe	144.5~155.5	337(M^+), 179(100%)	1
6	H	Me	Br	H	3-O-n-Pr	4-OMe	149~150	see Example 1	1
7	H	Me	Cℓ	H	3-O-n-Bu	4-OMe	158~159.5	351(M^+), 193(100%)	1
8	H	Me	Br	H	3-O-n-Bu	4-OMe	153~157	316(M^+-Br), 193(100%)	1
9	H	Me	Cℓ	H	3-O$(CH_2)_2$Ph	4-OMe	170~173	399(M^+), 241(100%)	1

Compound No.	R_1	R_2	X	Y	Z_1	Z_2	Melting point (°C)	MS(m/e)	Example No.
10	H	Me	Br	H	3-O$(CH_2)_2$Ph	4-OMe	158~159	443(M^+), 364(100%)	1
11	H	Me	Cℓ	H	H	4-Cℓ	179~180	283(M^+), 125(100%)	1
12	H	Me	Br	H	H	4-Cℓ	171~173	327(M^+), 248(100%)	1
13	H	Me	Cℓ	H	2-Me	4-Me	230~235	277(M^+), 119(100%)	1
14	H	Me	Br	H	2-Me	4-Me	210~218	242(M^+-Br), 119(100%)	1
15	H	Et	Cℓ	H	3-OEt	4-OMe	130~131.5	337(M^+), 165(100%)	1
16	H	Et	Br	H	3-OEt	4-OMe	130~131.5	302(M^+-Br,100%), 165	1
17	H	H	Cℓ	NO_2	3-OEt	4-OMe	187~188.5	354(M^+), 165(100%)	2
18	H	H	Br	NO_2	3-OEt	4-OMe	172~174	319(M^+-Br), 165(100%)	2
19	Et	H	Cℓ	NO_2	3-OEt	4-OMe	122~123	382(M^+), 165(100%)	2
20	Et	H	Br	NO_2	3-OEt	4-OMe	122~123	426(M^+), 165(100%)	2
21	Et	Me	Br	NO_2	3-OEt	4-OMe	97~98	440(M^+), 165(100%)	2
22	H	H	Cℓ	NO_2	3-O-n-Pr	4-OMe	169~171	see Example 2	2
23	H	H	Cℓ	NH_2	3-O-n-Pr	4-OMe	187.5~189.5	see Example 3	3
24	Et	H	Cℓ	NO_2	3-O-n-Pr	4-OMe	76~77	see Example 4	4
25	iPr	H	Cℓ	NO_2	3-O-n-Pr	4-OMe	82.5~84	see Example 5	5

0 275 997

Compound No.	R_1	R_2	X	Y	Z_1	Z_2	Melting point (°C)	MS(m/e)	Example No.
26	Allyl	H	Cℓ	NO_2	3-O-n-Pr	4-OMe	62.5~64	see Example 6	6
27	H	H	Br	NO_2	3-O-n-Pr	4-OMe	165~166.5	412(M^+), 179(100%)	2
28	Et	H	Br	NO_2	3-O-n-Pr	4-OMe	84~84.5	440(M^+), 179(100%)	4
29	H	H	Br	NO_2	3-O-n-Bu	4-OMe	130~132	426(M^+), 193(100%)	2
30	H	H	Br	NH_2	3-O-n-Bu	4-OMe	155~159	396(M^+), 193(100%)	3
31	Et	H	Br	NO_2	3-O-n-Bu	4-OMe	55~56	454(M^+), 193(100%)	4
32	Et	H	Br	NH_2	3-O-n-Bu	4-OMe	108~110.5	see Example 7	7, 3
33	H	H	Br	NO_2	3-O-n-Hex	4-OMe	138~141	454(M^+), 221(100%)	2
34	H	H	Br	NH_2	3-O-n-Hex	4-OMe	171~173	424(M^+), 221(100%)	3
35	iPr	H	Br	NO_2	3-O-n-Hex	4-OMe	57~58.5	496(M^+), 417(100%)	5
36	H	H	Cℓ	NO_2	3-O$(CH_2)_2$Ph	4-OMe	149~150.5	430(M^+), 105(100%)	2
37	H	H	Cℓ	NH_2	3-O$(CH_2)_2$Ph	4-OMe	192~194.5	400(M^+), 241(100%)	3
38	Et	H	Cℓ	NO_2	3-O$(CH_2)_2$Ph	4-OMe	oily substance	458(M^+), 105(100%)	4
39	H	H	Cℓ	NO_2	H	4-NMe_2	147.5~149.5	323(M^+), 134(100%)	2
40	H	H	Cℓ	NH_2	H	4-NMe_2	118~123	293(M^+), 134(100%)	3
41	H	Me	Br	NO_2	H	4-Cℓ	215~219	372(M^+), 125(100%)	2

Compound No.	R_1	R_2	X	Y	Z_1	Z_2	Melting point (°C)	MS(m/e)	Example No.
42	Et	Me	Br	NO_2	H	4-Cℓ	Oily substance	400(M^+), 125(100%)	4
43	Et	H	Cℓ	OH	3-O-n-Pr	4-OMe	73~74	see Example 8	8
44	Et	H	Cℓ	OH	3-O-n-Bu	4-OMe	77~78	381(M^+), 193(100%)	8
45	Et	H	Cℓ	OMe	3-OEt	4-OMe	103~105	367(M^+), 165(100%)	9 – ii)
46	Et	H	Cℓ	OEt	3-OEt	4-OMe	80.5~81.5	381(M^+), 165(100%)	9 – ii)
47	Et	H	Br	OMe	3-OEt	4-OMe	88~89	411(M^+), 332(100%)	9 – ii)
48	Et	H	Br	OEt	3-OEt	4-OMe	67.5~69	425(M^+), 346(100%)	9 – ii)
49	Et	H	Cℓ	OMe	3-O-n-Pr	4-OMe	92~93	381(M^+), 179(100%)	9 – i)
50	Et	H	Cℓ	OEt	3-O-n-Pr	4-OMe	77.5~78	see Example 9	9 – i), ii)
51	Et	H	Cℓ	O-i-Pr	3-OEt	4-OMe	Oily substance	395(M^+), 165(100%)	9 – ii)
52	Et	H	Br	O-i-Pr	3-OEt	4-OMe	Oily substance	439(M^+), 360(100%)	9 – ii)
53	Et	H	Cℓ	O-i-Pr	3-O-n-Pr	4-OMe	Oily substance	409(M^+), 179(100%)	9 – ii)

Compound No.	R_1	R_2	X	Y	Z_1	Z_2	Melting point (°C)	MS(m/e)	Example No.
54	Et	H	Cℓ	O	3-O-n-Pr	4-OMe	Oily substance	407(M^+),179(100%)	9-(ii)
55	Et	H	Cℓ	O	3-OEt	4-OMe	Oily substance	395(M^+),165(100%)	9-(ii)
56	Et	H	Br	O	3-OEt	4-OMe	Oily substance	439(M^+),165(100%)	9-(ii)
57	Et	H	Cℓ	O-n-Pr	3-O-n-Pr	4-OMe	Oily substance	409(M^+),179(100%)	9-(ii)
58	Et	H	Br	O	3-OEt	4-OMe	98.5~100	435(M^+),165(100%)	9-(ii)
59	Et	H	Br	O-n-Hex	3-OEt	4-OMe	89~91.5	481(M^+),165(100%)	9-(ii)
60	Et	H	Br	OMe	3-OEt	4-OMe	Oily substance	451(M^+),165(100%)	9-(ii)
61	Et	H	Br	OMe	3-OEt	4-OMe	Oily substance	451(M^+),165(100%)	9-(ii)
62	Et	H	Cℓ	Cℓ	3-O-n-Pr	4-OMe	101~103	see Example 11	11
63	H	H	Cℓ	O-i-Pr	3-OMe	4-OMe	173~174	353(M^+),151(100%)	12
64	H	H	Cℓ	OEt	3-OEt	4-OMe	186.5~188	353(M^+),165(100%)	12
65	H	H	Cℓ	O-i-Pr	3-OEt	4-OMe	149.5~150	367(M^+),165(100%)	12
66	H	H	Cℓ	OEt	3-O-n-Pr	4-OMe	145~146	367(M^+),179(100%)	12
67	H	H	Cℓ	O-i-Pr	3-O-n-Pr	4-OMe	103~104	381(M^+),179(100%)	12
68	H	H	Cℓ	OEt	3-O-n-Bu	4-OMe	117~118	see Example 12	12
69	H	H	Cℓ	O-i-Pr	3-O-n-Bu	4-OMe	105~106	395(M^+),193(100%)	12
70	H	H	Cℓ	Cℓ	3-OEt	4-OMe	155~156	343(M^+),165(100%)	10

Compound No.	R_1	R_2	X	Y	Z_1	Z_2	Melting point (℃)	MS(m/e)	Example No.
71	H	H	Cℓ	Cℓ	3-O-n-Pr	4-OMe	181～183	see Example 10	10
72	H	H	Cℓ	O-i-Pr	3-O-n-Hex	4-OMe	84～87	423(M^+),221(100%)	10
73	Et	Me	Br	OMe	3-OEt	4-OMe	Oily substance	425(M^+),346(100%)	9-(ii)
74	Et	Me	Br	OEt	3-OEt	4-OMe	81.5～84	439(M^+),165(100%)	9-(ii)
75	Et	H	Cℓ	OCH_2Ph	3-O-n-Pr	4-OMe	Oily substance	457(M^+),366(100%)	9-(i)
76	iPr	H	Cℓ	OMe	3-O-n-Pr	4-OMe	108～110	395(M^+),179(100%)	9-(ii)
77	iPr	H	Cℓ	OEt	3-O-n-Pr	4-OMe	Oily substance	409(M^+,100%)	9-(ii)
78	iPr	H	Cℓ	O-i-Pr	3-O-n-Pr	4-OMe	Oily substance	423(M^+),188(100%)	9-(ii)
79	iPr	H	Cℓ	O⌒	3-O-n-Pr	4-OMe	Oily substance	421(M^+,100%)	9-(ii)
80	H	H	Cℓ	OMe	3-OEt	4-OMe	184～186.5	339(M^+),165(100%)	13
81	Et	H	Cℓ	OPh	3-OEt	4-OMe	77～82	429(M^+,100%)	9-(ii)
82	H	H	Cℓ	O-i-Pr	2-O-n-Pr	H	138～144	351(M^+),149(100%)	12
83	H	H	Cℓ	O-i-Pr	2-O-n-Pr	4-OMe	126～127.5	381(M^+),179(100%)	12
84	H	H	Cℓ	OEt	3-OMe	4-OMe	182～185	339(M^+),151(100%)	12
85	H	H	Cℓ	OCH_2Ph	3-OMe	4-OMe	179～180	401(M^+), 91(100%)	12
86	H	H	Cℓ	OCH_2Ph	3-OEt	4-OMe	182～185	415(M^+),165(100%)	12
87	H	H	Cℓ	NO_2	3-OMe	4-OMe	205～208	340(M^+),151(100%)	2

Compound No.	R_1	R_2	X	Y	Z_1	Z_2	Melting point (°C)	MS(m/e)	Example No.
88	H	H	Cℓ	O-sec-Bu	3-OEt	4-OMe	130.5~132	see Example 13	13
89	H	H	Cℓ	O-sec-Bu	3-OMe	4-OMe	151~153	367(M⁺), 151(100%)	13
90	H	H	Cℓ	OCH(Me)Me	3-OMe	4-OMe	126~127	415(M⁺), 105(100%)	12
91	H	H	Cℓ	OCH(Ph)Me	3-OEt	4-OMe	95~96	429(M⁺), 105(100%)	12
92	H	H	Cℓ	S-n-Pr	3-OMe	4-OMe	129~130	see Example 14	14
93	H	H	Cℓ	S-i-Pr	3-OMe	4-OMe	179~180	369(M⁺), 151(100%)	14
94	H	H	Cℓ	S-i-Bu	3-OMe	4-OMe	154.5~155	383(M⁺), 151(100%)	14
95	H	H	Cℓ	O-sec-Bu	3-OMe	4-OMe	169~170	383(M⁺), 151(100%)	14

Now, Formulation Examples of the compounds of the formula I will be given.

FORMULATION EXAMPLES 1 and 2 (Tablets)

Compound No. 53 (Formulation Example 1)	10 g
or Compound No. 68 (Formulation Example 2)	
Lactose	20 g
Starch	4 g
Starch for paste	1 g
Magnesium stearate	100 mg
Carboxymethyl cellulose calcium	7 g
Total	42.1 g

The above components were mixed in a usual manner, and formulated into sugar-coated tablets each containing 50 mg of an active ingredient.

FORMULATION EXAMPLES 3 and 4 (Capsules)

Compound No. 52 (Formulation Example 3)	10 g
or Compound No. 69 (Formulation Example 4)	
Lactose	20 g
Crystal cellulose powder	10 g
Magnesium stearate	1 g
Total	41 g

The above components were mixed in a usual manner, and filled into gelatin capsules to obtain capsules each containing 50 mg of an active ingredient.

FORMULATION EXAMPLES 5 and 6 (Soft capsules)

Compound No. 48 (Formulation Example 5)	10 g
or Compound No. 91 (Formulation Example 6)	
Corn Oil	35 g
Total	45 g

The above components were mixed and formulated in a usual manner to obtain soft capsules.

FORMULATION EXAMPLES 7 and 8 (Ointment)

Compound No. 51 (Formulation Example 7)	1.0 g
or Compound No. 89 (Formulation Example 8)	
Olive oil	20 g
White vaseline	79 g
Total	100 g

The above components were mixed in a usual manner to obtain 1% ointment.

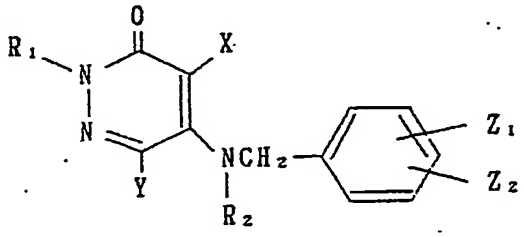
FORMULATION EXAMPLES 9 and 10 (Aerosol suspension)

(A) Compound No. 33 (Formulation Example 9) or Compound No. 67 (Formulation Example 10) 0.25(%)
Isopropyl myristate 0.10
Ethanol 26.40
(B) A 60-40% mixture of 1,2-dichlorotetrafluoroethane and 1-chloropentafluoroethane 73.25

The above composition (A) was mixed. The solution mixture thereby obtained was charged in a container equipped with a valve, and the propellant (B) was injected from a valve nozzle to a gauge pressure of from about 2.46 to 2.81 mg/cm^2 to obtain an aerosol suspension.

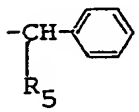
Claims

1. A 3(2H)pyridazinone of the formula:



(I)

wherein R_1 is hydrogen, 2-propenyl or straight chained or branched C_1-C_4 alkyl; R_2 is hydrogen or C_1-C_3 alkyl; X is chlorine or bromine; Y is hydrogen, nitro, -NHR_3 wherein R_3 is hydrogen or straight chained or branched C_1-C_4 alkyl, -AR_4 wherein A is oxygen or sulfur and R_4 is hydrogen, straight chained or branched C_1-C_8 alkyl, C_3-C_8 alkenyl having one double bond, C_3-C_6 alkynyl having one triple bond, phenyl or



wherein R_5 is hydrogen or C_1-C_4 alkyl, or halogen; Z_1 is hydrogen, C_1-C_4 alkyl, -OR_6 wherein R_6 is hydrogen, straight chained or branched C_1-C_8 alkyl or

EMI PA = 75 FR = 3 HE = 15 WI = 35 TI = CHE

wherein n is an integer of from 1 to 4, $-N(R_7)_2$ wherein R_7 is C_1-C_4 alkyl, or halogen; Z_2 is C_1-C_4 alkyl, $-OR_6$ wherein R_6 is as defined above, $-N(R_7)_2$ wherein R_7 is as defined above, or halogen, provided that when R_1 is straight chained or branched C_2-C_4 alkyl, Y is not hydrogen and when R_1 is hydrogen, methyl or 2-propenyl, Y and R_2 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, wherein Z_2 is $-OR_6$ wherein R_6 is as defined above, $-N(R_7)_2$ wherein R_7 is as defined above, or halogen.

3. The compound according to Claim 2, wherein R_2 is hydrogen.

4. The compound according to Claim 3, wherein R_1 is hydrogen, 2-propenyl, ethyl or isopropyl.

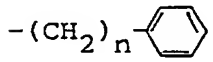
5. The compound according to Claim 4, wherein Y is nitro, amino, $-AR_4$ wherein A and R_4 are as defined above, or halogen.

6. The compound according to Claim 5, wherein halogen is chlorine.

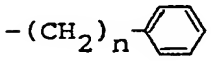
7. The compound according to Claim 6, wherein Z_1 is hydrogen, C_1-C_4 alkyl, $-OR_6$ wherein R_6 is as defined above, $-N(CH_3)_2$ or chlorine, and Z_2 is $-OR_6$ wherein R_6 is as defined above, $-N(CH_3)_2$ or chlorine.

8. The compound according to Claim 7, wherein R_1 is hydrogen, ethyl or isopropyl.

9. The compound according to Claim 8, wherein Z_1 is hydrogen or $-OR_6$ wherein R_6 is straight chained C_1-C_8 alkyl or

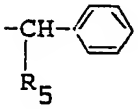


wherein n is as defined above, and Z_2 is $-OR_6$ wherein R_6 is straight chained C_1-C_8 alkyl or



wherein n is as defined above.

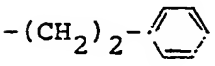
10. The compound according to Claim 9, wherein Y is $-OR_4$ wherein R_4 is straight chained or branched C_1-C_6 alkyl, C_3-C_6 alkenyl having one double bond, C_3-C_6 alkynyl having one triple bond, phenyl or



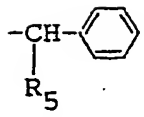
wherein R_5 is as defined above.

11. The compound according to Claim 10, wherein R_1 is hydrogen.

12. The compound according to Claim 11, wherein each of Z_1 and Z_2 which may be the same or different is $-OR_6$ wherein R_6 is straight chained C_1-C_6 alkyl or

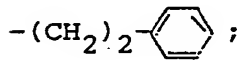


13. The compound according to Claim 12, wherein Y is $-OR_4$ wherein R_4 is straight chained or branched C_1-C_6 alkyl, $-CH_2C(R_4') = C(R_4'')(R_4''')$ wherein each of R_4', R_4'' and R_4''' which may be the same or different is hydrogen or methyl, $-CH_2C \equiv C\text{-}R_4'$ wherein R_4' is as defined above, phenyl or



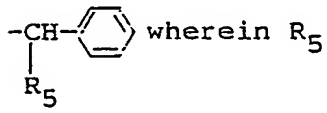
wherein R_5 is hydrogen or C_1-C_4 alkyl.

14. The compound according to Claim 13, wherein Z_1 is 3-OR_6 wherein R_6 is straight chained C_1-C_6 alkyl or



and Z_2 is 4-OCH_3.

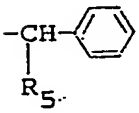
15. The compound according to Claim 14, wherein Y is -OR_4 wherein R_4 is straight chained or branched C_1-C_6 alkyl, 2-propenyl, propargyl methyl, phenyl or



wherein R_5 is hydrogen or methyl.

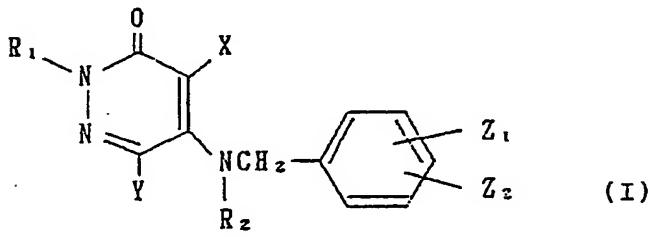
16. The compound according to Claim 15, wherein X is chlorine.

17. The compound according to Claim 16, wherein Y is -OR_4 wherein R_4 is straight chained or branched C_1-C_4 alkyl or



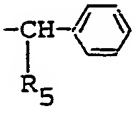
wherein R_5 is hydrogen or methyl.

18. A process for producing a 3(2H)pyridazinone of the formula:



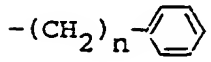
(I)

wherein R_1 is hydrogen, 2-propenyl or straight chained or branched C_1-C_4 alkyl; R_2 is hydrogen or C_1-C_3 alkyl; X is chlorine or bromine; Y is hydrogen, nitro, -NHR_3 wherein R_3 is hydrogen or straight chained or branched C_1-C_4 alkyl, -AR_4 wherein A is oxygen or sulfur and R_4 is hydrogen, straight chained or branched C_1-C_6 alkyl, C_3-C_6 alkenyl having one double bond, C_3-C_6 alkynyl having one triple bond, phenyl or



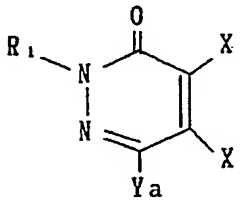
wherein R_5 is hydrogen or C_1-C_4 alkyl, or halogen; Z_1 is hydrogen, C_1-C_4 alkyl, -OR_6 wherein R_6 is

hydrogen, straight chained or branched C_1-C_8 alkyl or



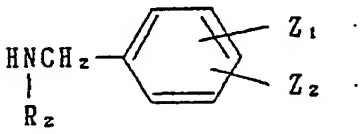
wherein n is an integer of from 1 to 4, $-N(R_7)_2$ wherein R_7 is C_1-C_4 alkyl, or halogen; Z_2 is C_1-C_4 alkyl, $-OR_8$ wherein R_8 is as defined above, $-N(R_7)_2$ wherein R_7 is as defined above, or halogen, provided that when R_1 is straight chained or branched C_2-C_4 alkyl, Y is not hydrogen and when R_1 is hydrogen, methyl or 2-propenyl, Y and R_2 are not simultaneously hydrogen, or a pharmaceutically acceptable salt thereof, which comprises:

(a) reacting a compound of the formula:



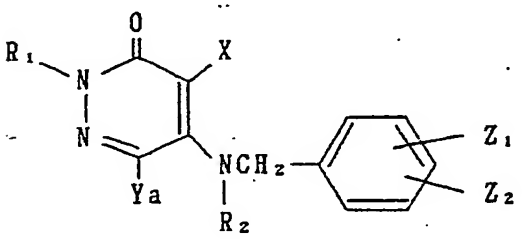
(II)

wherein R_1 and X are as defined above, and Ya is hydrogen, nitro, amino, $-OR_4$ wherein R_4 is as defined above, or halogen, with a compound of the formula:



(III)

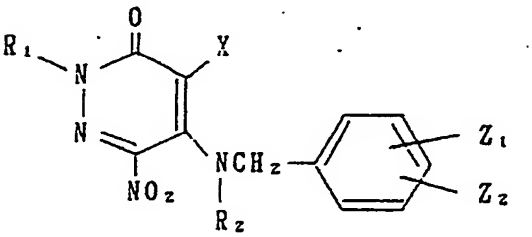
wherein R_2, Z_1 and Z_2 are as defined above, or its salt, if necessary in the presence of a acid binding agent, to obtain a 3(2H)pyridazinone of the formula:



(IA)

wherein R_1, R_2, Z_1, Z_2, X and Ya are as defined above; or

(b) reacting a compound of the formula:

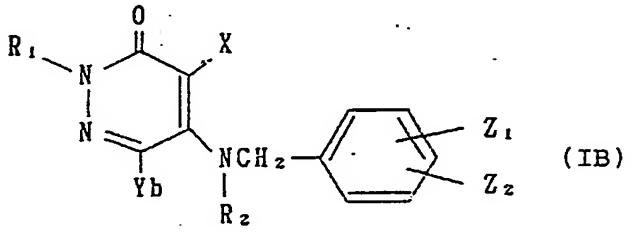


(IB-a)

wherein R_1, R_2, X, Z_1 and Z_2 are as defined above, with a compound of the formula:

M^+Yb^- (IV)

wherein M is alkali metal, and Yb is -NHR_3 wherein R_3 is as defined above or -AR_4 wherein A and R_4 are as defined above, to obtain a 3(2H)pyridazinone of the formula:



(IB)

wherein R_1, R_2, Z_1, Z_2, X and Yb are as defined above.

19. An antagonistic agent against SRS-A comprising an effective amount of a 3(2H)pyridazinone of the formula I as defined in Claim 1 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

20. A method of reducing the incidence or severity of allergy induced in a subject by SRS-A, which comprises administering to said subject an amount effective to reduce the incidence or severity of the allergy of a 3(2H)pyridazinone as defined in Claim 1 or a pharmaceutically acceptable salt thereof.

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Professional
Representative
before the European
Patent Office

February 8, 1988

Re: European Patent Application
No. 88 100 798.3
Nissan Chemical Industries Ltd.
Our Ref.: EA-6265

In the specification of the above-identified European patent application, some errors have been found. It is respectfully requested that the following corrections be made prior to the publication of the application:

Page 17: after "salt", the term --of the formula IV-- should be inserted.

Page 18: in line 1, the term "a metal amide" should read --an alkali metal amide--;
in line 2, the term "a metal alkoxide" should read --an alkali metal alkoxide--; and
in line 3, the term "defined by above R_3 and R_4" should be deleted.

Amended replacement pages 17 and 18 are enclosed in triplicate.

Respectfully submitted,

Günter Wächtershäuser
Patent Attorney

Enclosures
Replacement pages, tripl.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 88100798.3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP - A2 - 0 193 853 (NISSAN) * Claims 1,7,8 * --	1,18,19	C 07 D 237/22 A 61 K 31/50
D,A	EP - A1 - 0 186 817 (NISSAN) * Claims 1,7,8 * --	1,18,19	
A	US - A - 4 296 120 (KADIN) * Abstract; claim 1 * ----	1,19	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 237/00
C 07 D 207/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-19
Claims searched incompletely: -
Claims not searched: 20
Reason for the limitation of the search: Method for treatment of the human or animal body by therapys, article 52 (4) EPC

Place of search	Date of completion of the search	Examiner
VIENNA	25-04-1988	LUX

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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